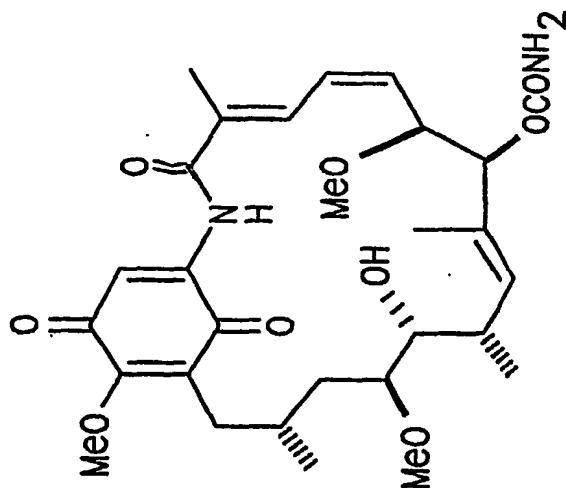
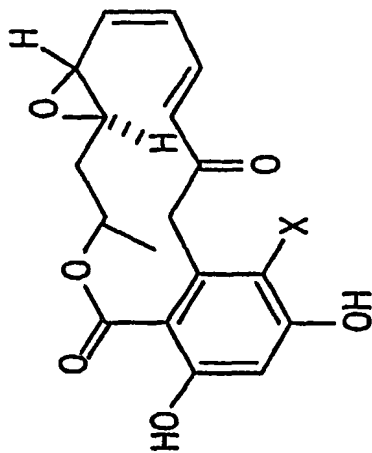


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FIG. 1



Geldanamycin (3)



X=Cl Radical (1)

X=H Monocillin I (2)

FIG. 2

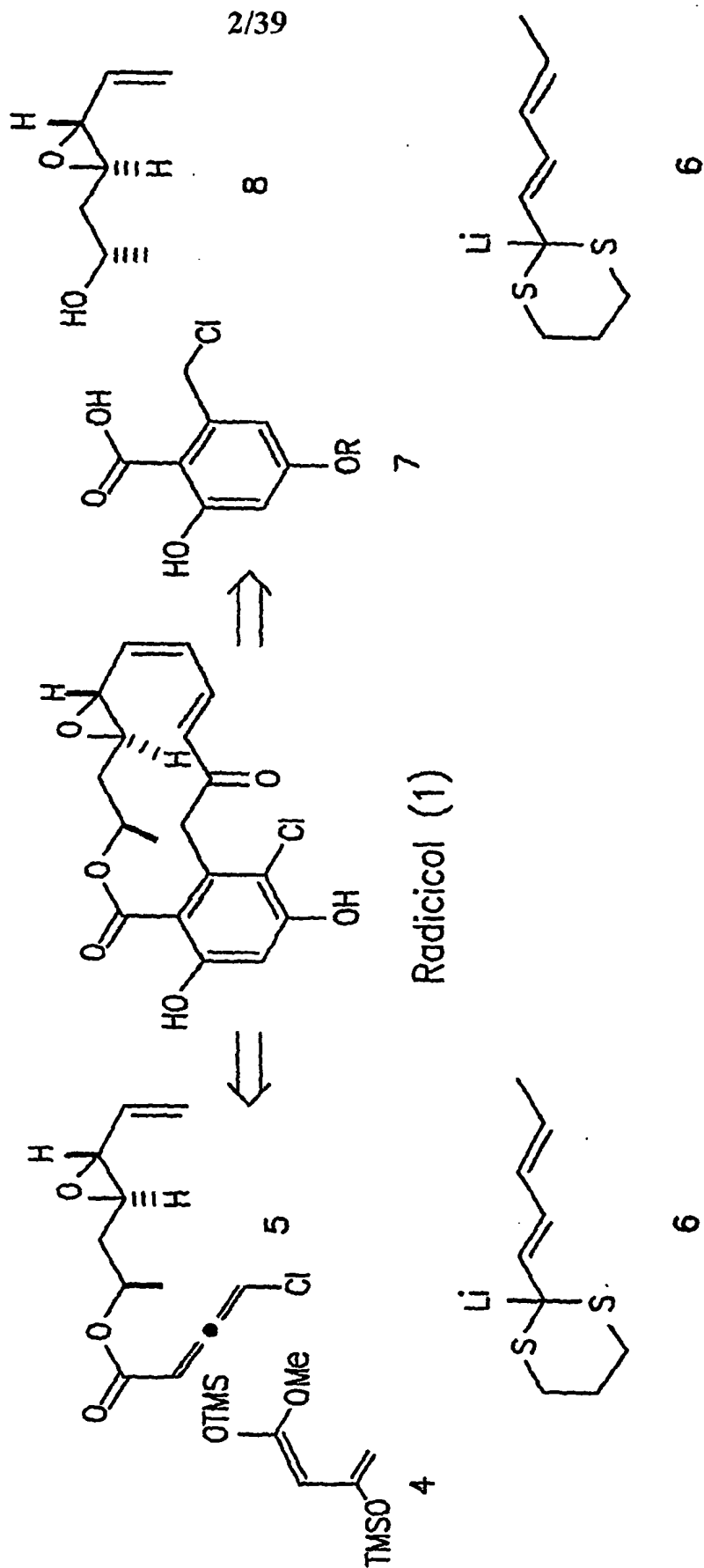
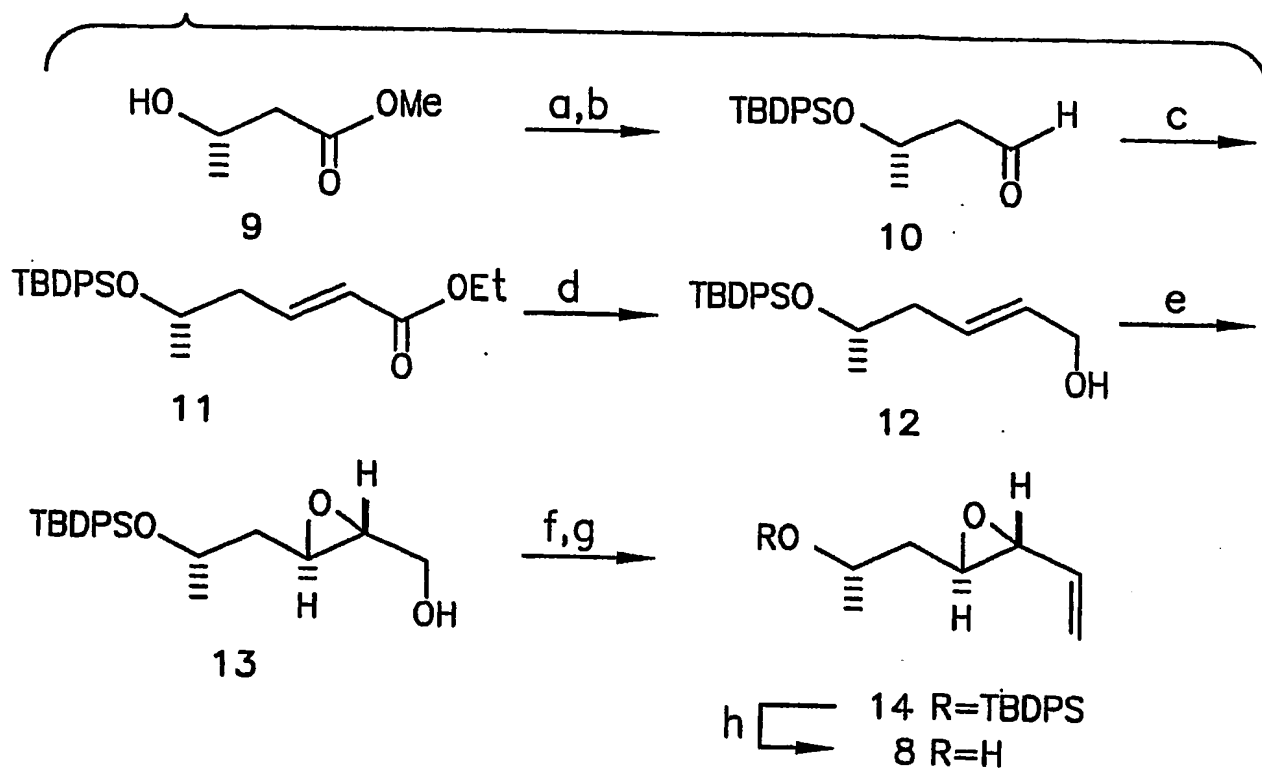


FIG. 3

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- (a) TBDPSCI, imid., >95%; (b) DIBAL-H, -78 °C, 92%;
 (c) LiCl, DIPEA $(\text{EtO})_2\text{P}(\text{O})\text{CH}_2\text{CO}_2\text{Et}$, 95%;
 (d) DIBAL-H, -20 °C, 96%; (e) (+)-DET, $\text{Ti}(\text{O}i\text{Pr})_4$, TBHP, 90%, >95% ee; (f) $\text{SO}_3^*\text{pyridine}$, Et_3N , DMSO, 90%;
 (g) $\text{PH}_3\text{PCH}_3\text{Br}$, NaHMDS, 0 °C, 82%; (h) TBAF, 89%.

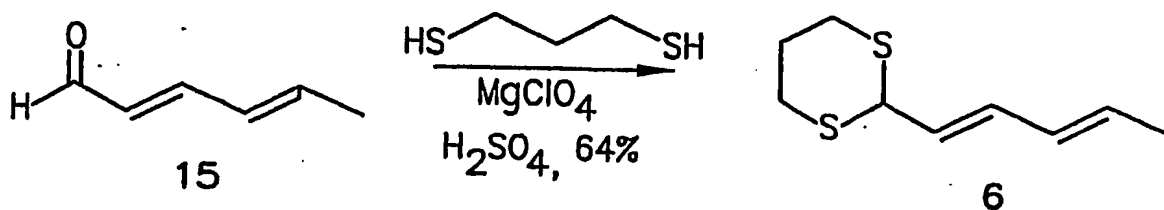
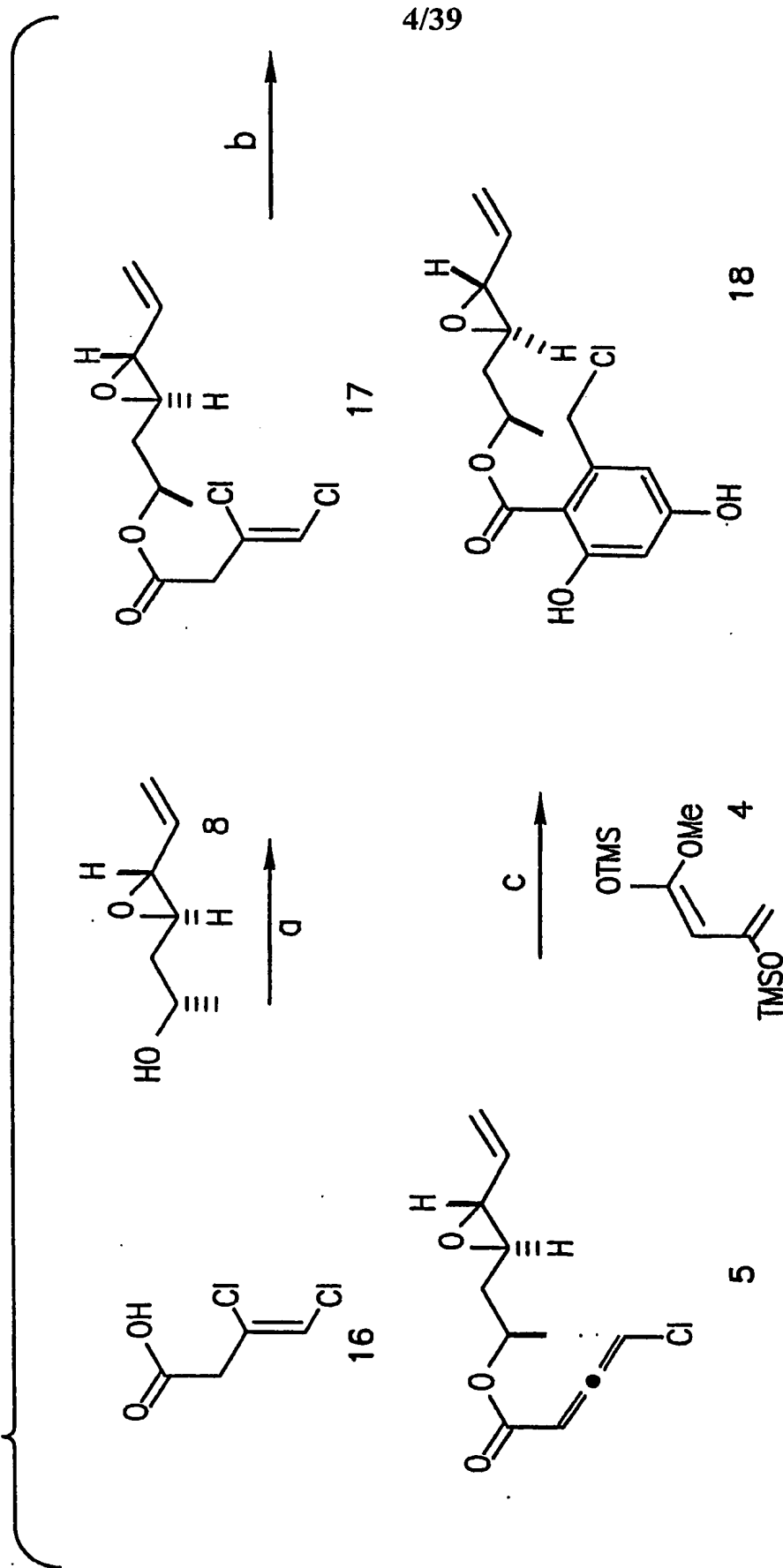


FIG. 4



(a) DEAD, PPh_3 , 70%; (b.) $i\text{Pr}_2\text{NEt}$, 70%; (c.) 50% (4:1)

FIG. 5

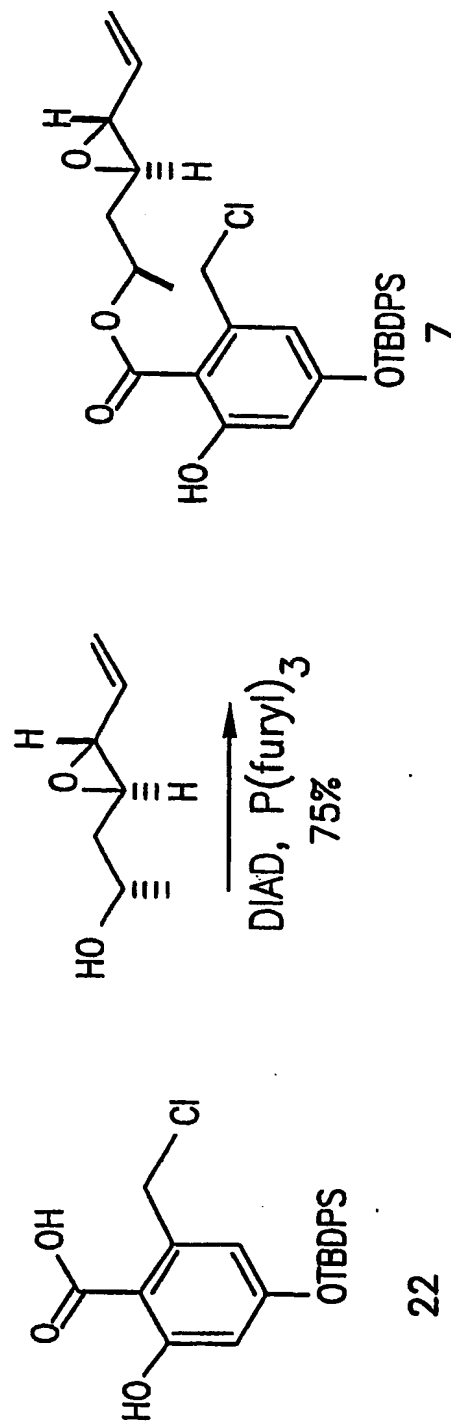
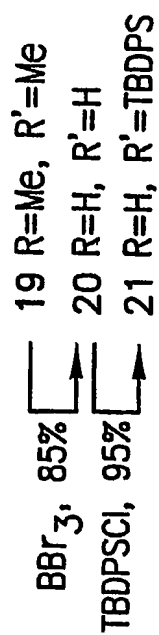
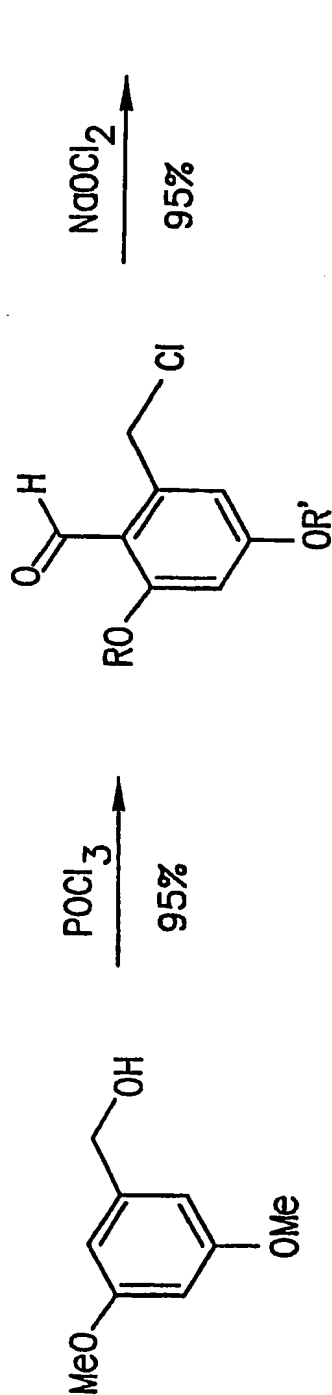
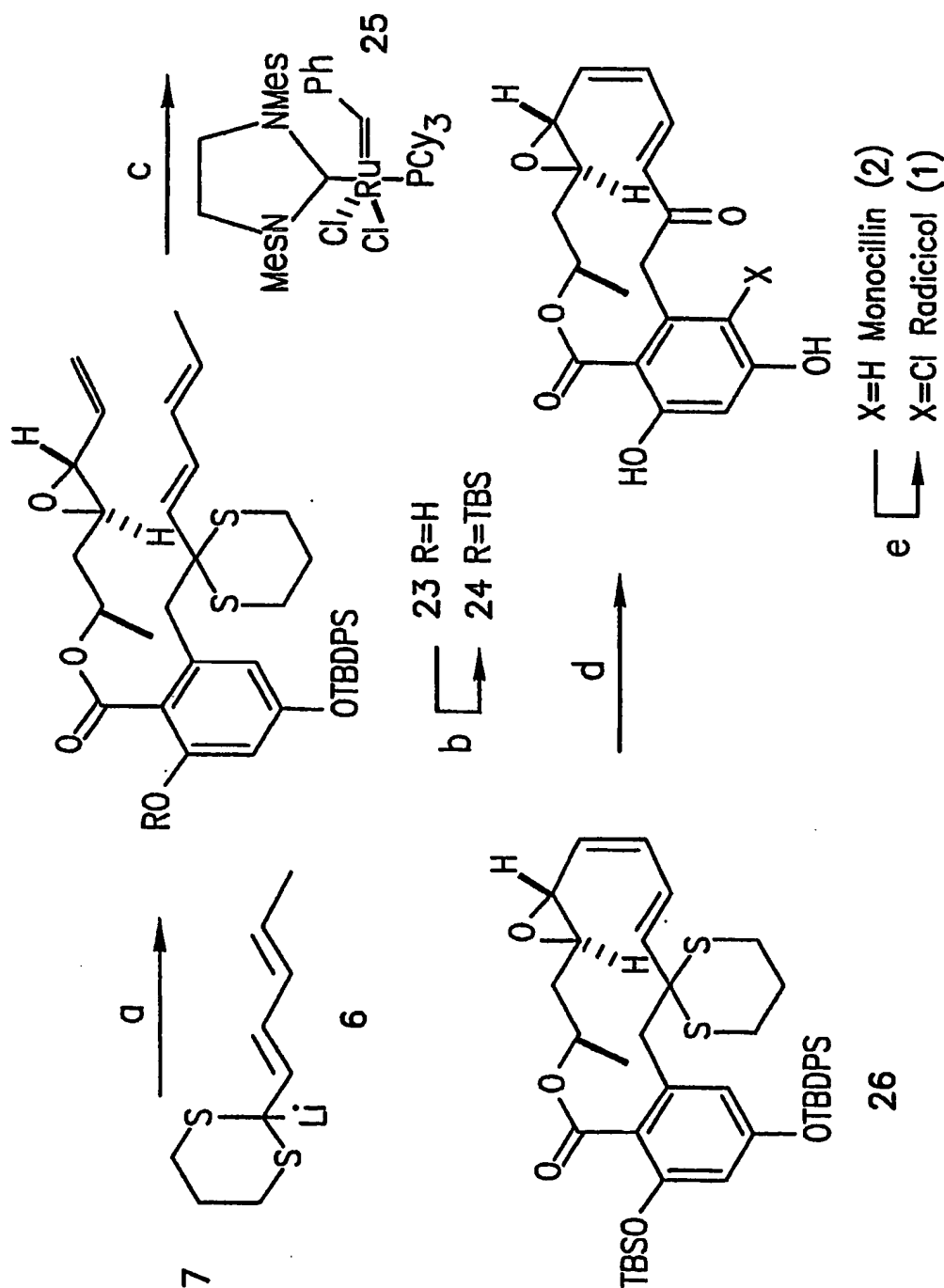


FIG. 6



a. n-BuLi, -78°C , 50% (6:1); b. TBSCl, 83%; c. 42 C, 70%; d. (i) mCPBA, (ii) Ac_2O , Et_3N , H_2O , 60°C , (iii) NaHCO_3 , MeOH, 60%; e. SO_2Cl_2 , 50%

FIG. 7

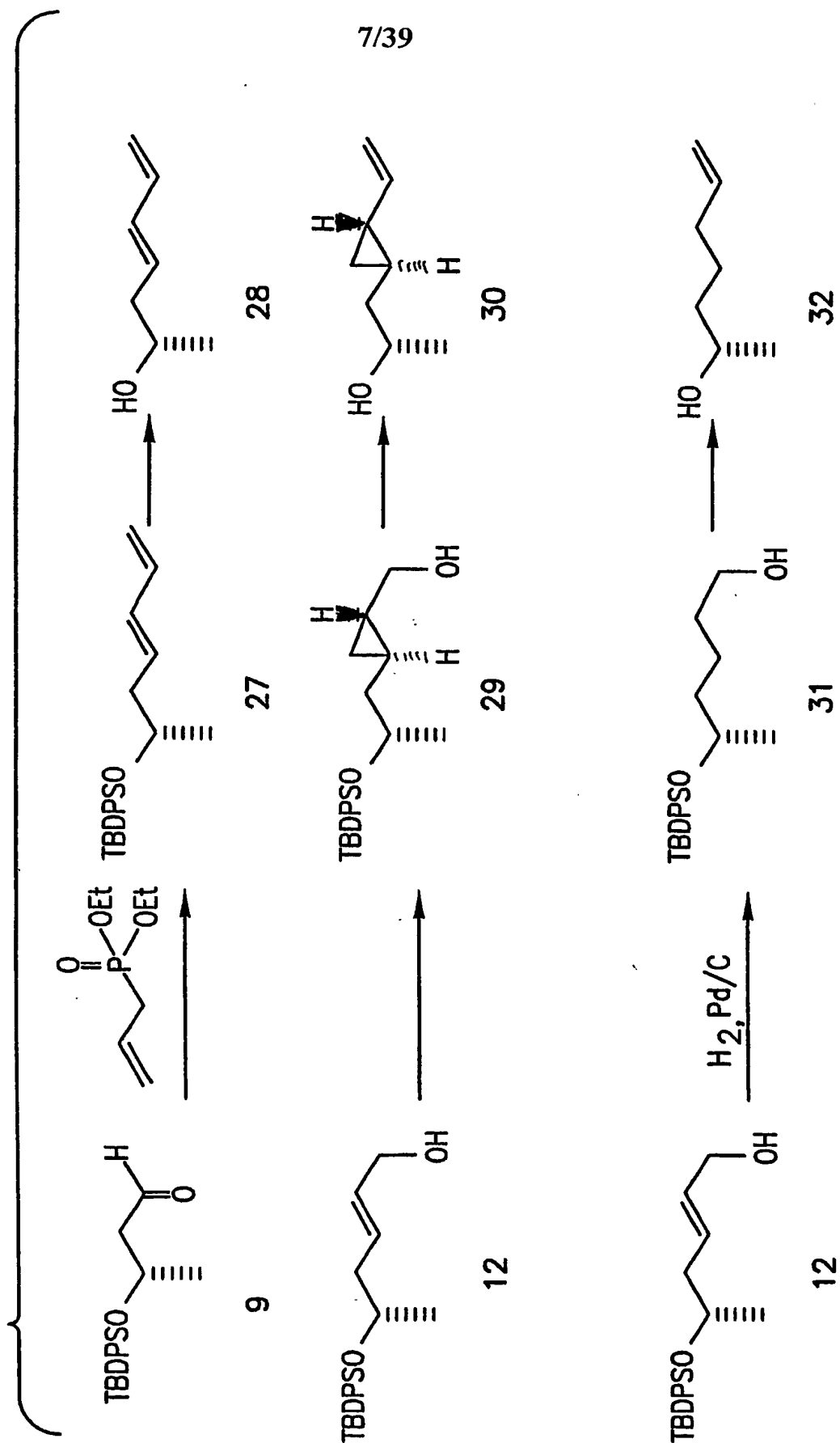


FIG. 8

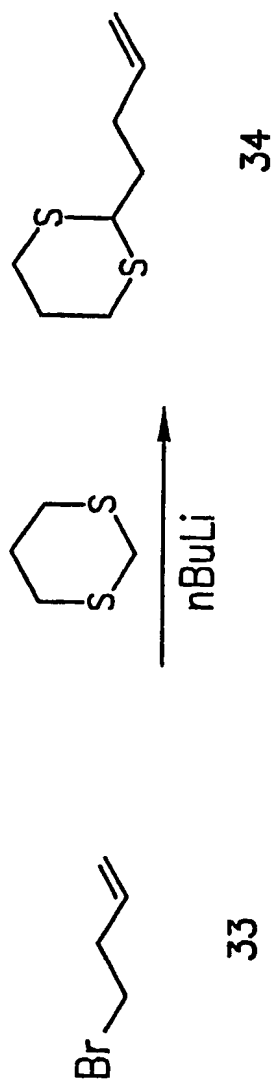


FIG. 9

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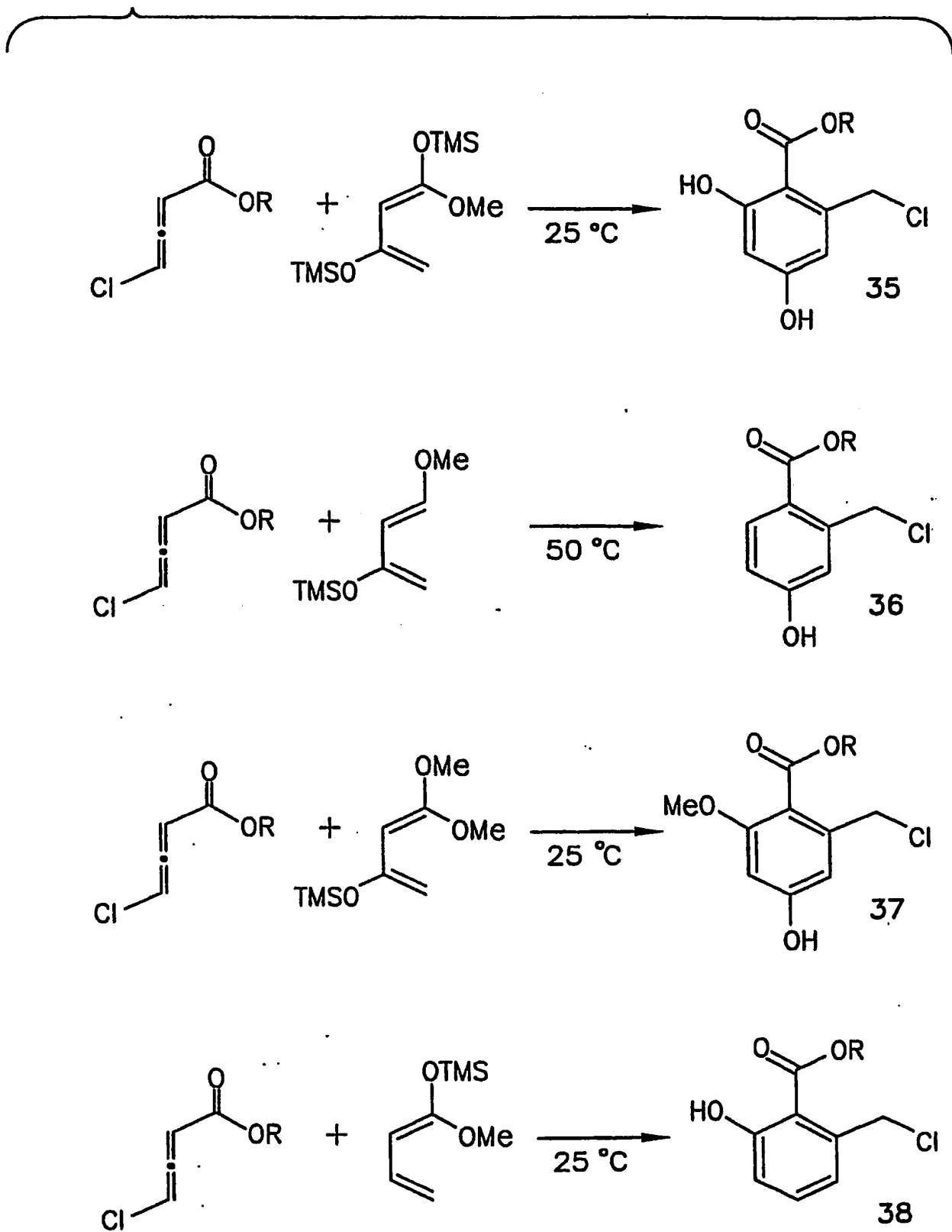
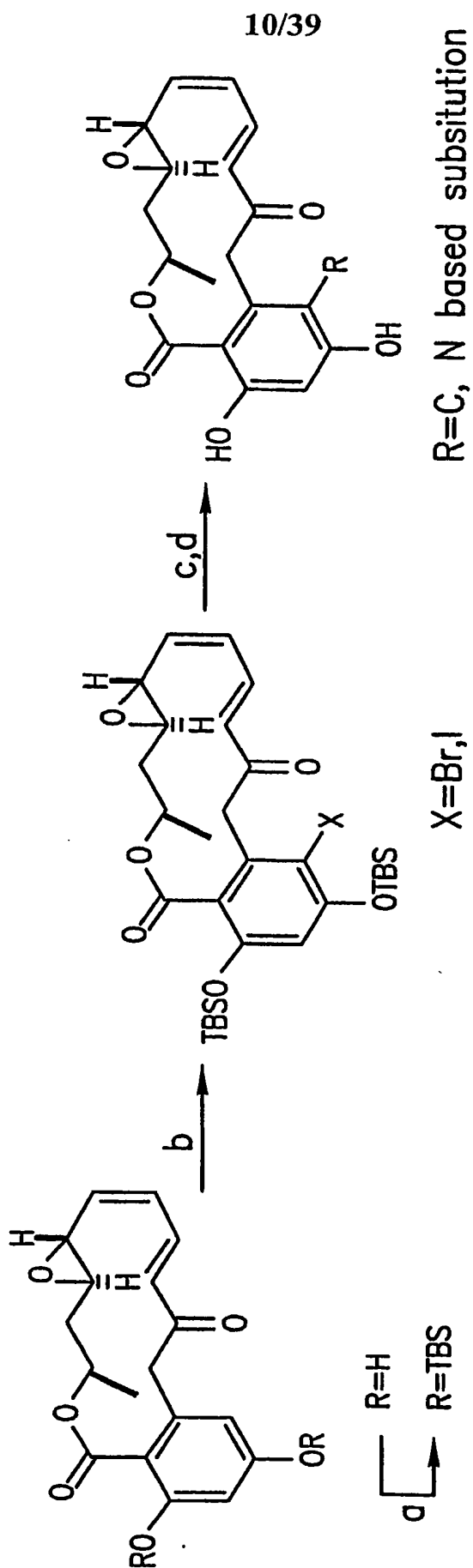
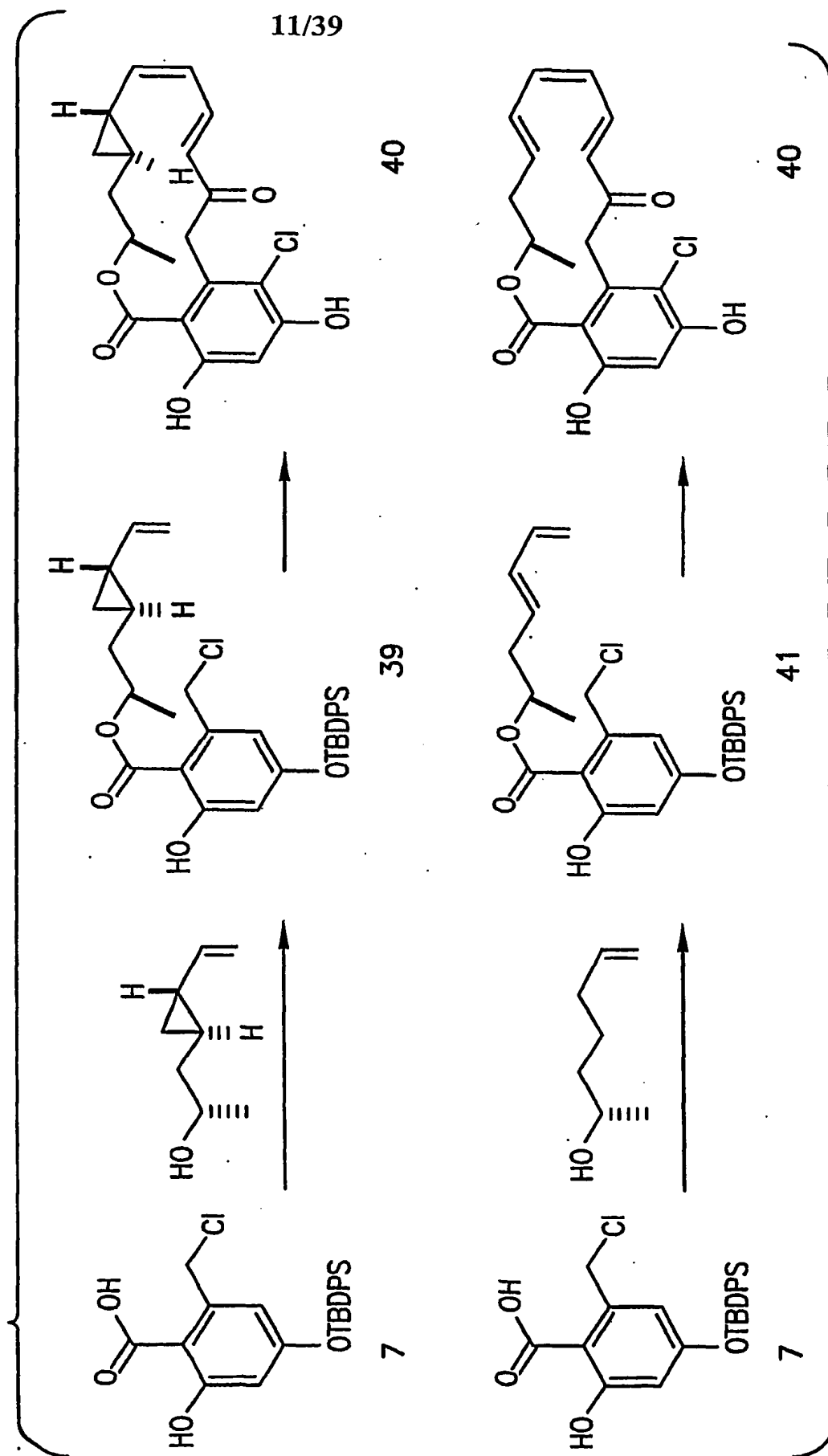


FIG. 10



a. TBSCl, pyridine; b. NIS or NBS, TsOH; c. Pd(PPh)₃, RSnBu₃, d. nBu₄NF

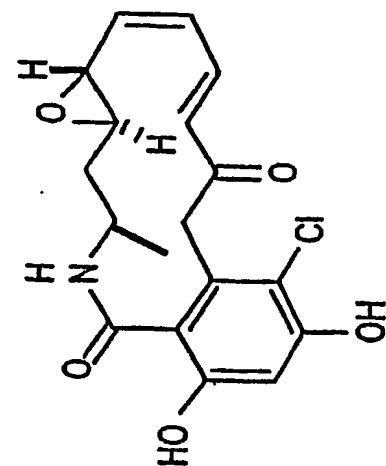
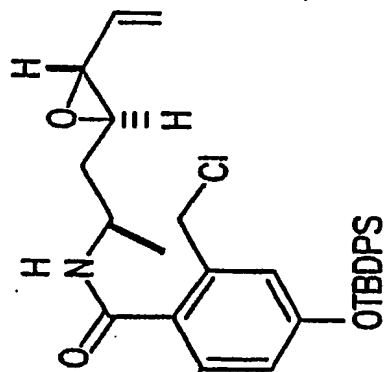
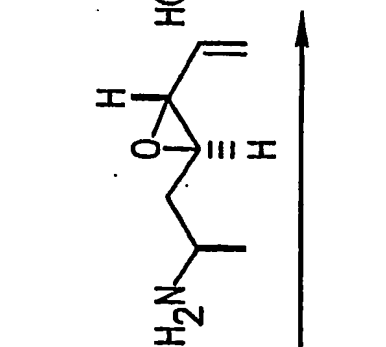
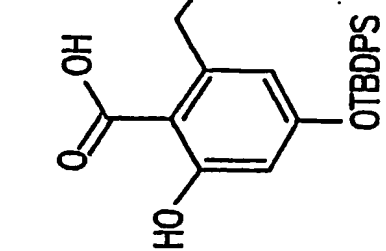
FIG. 11-1



TO FIG. 11-2

FROM FIG. 11-1

FIG. 11-2

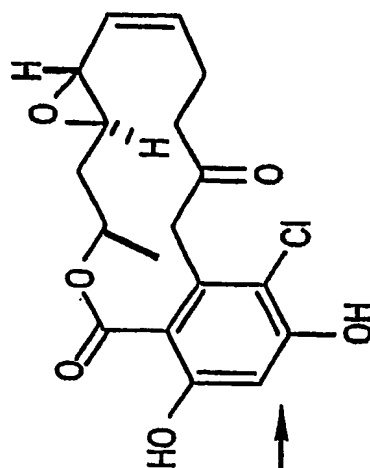
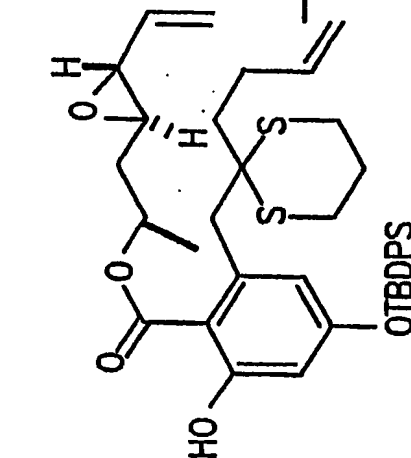
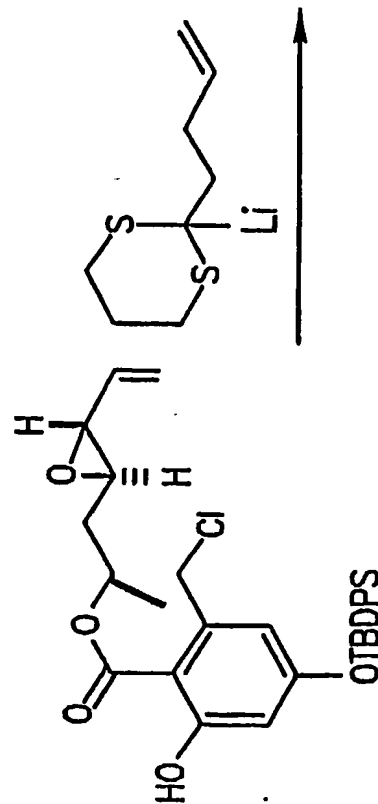


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39

7

44

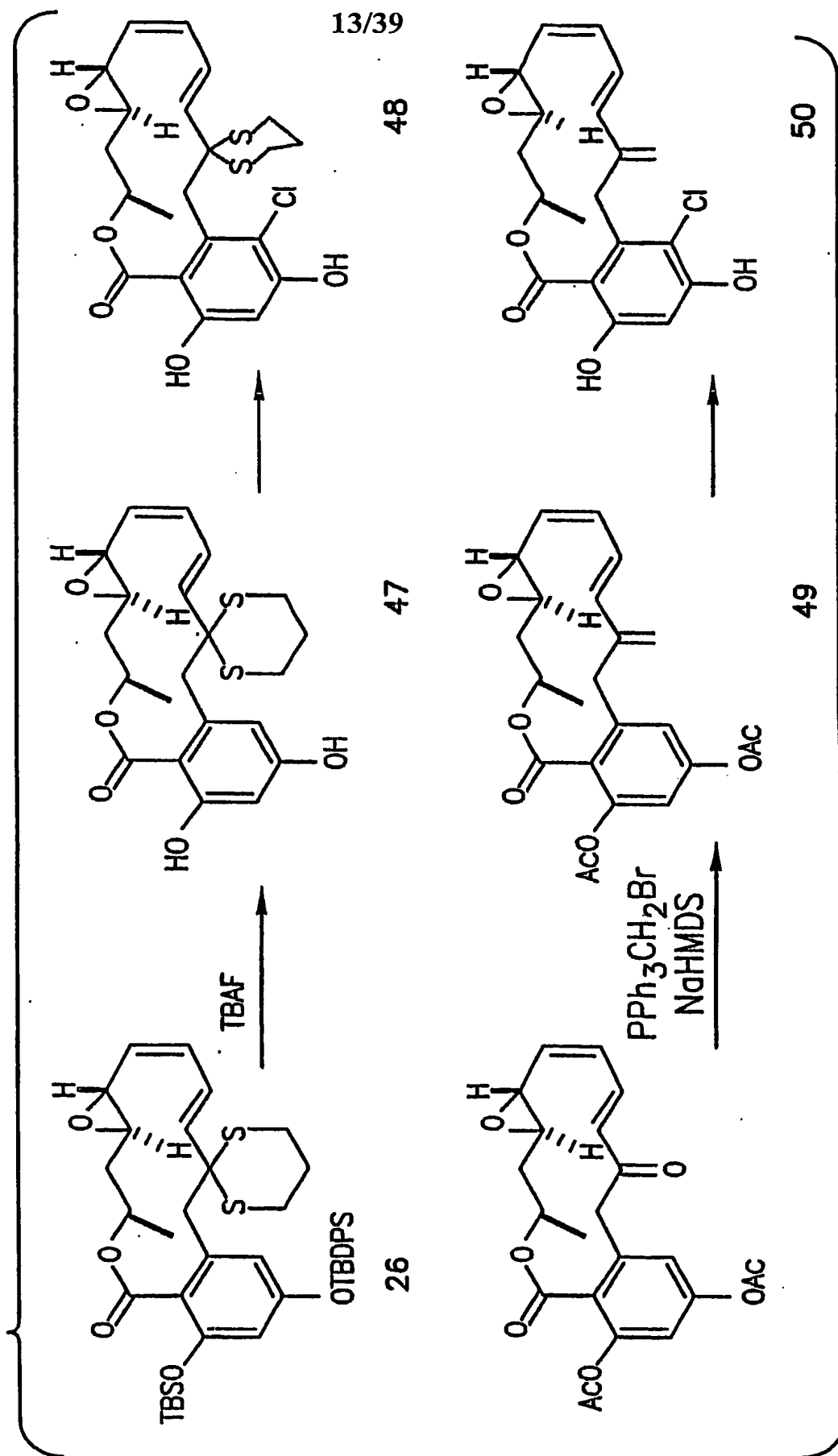


22

45

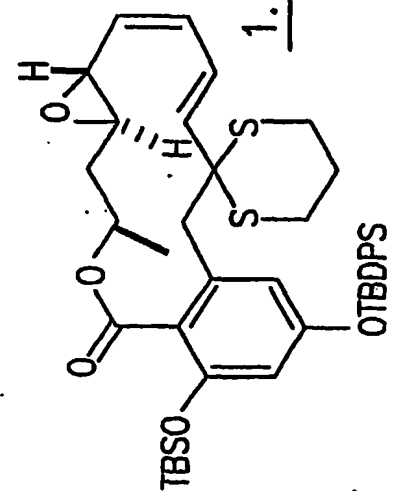
46

FIG. 12-1

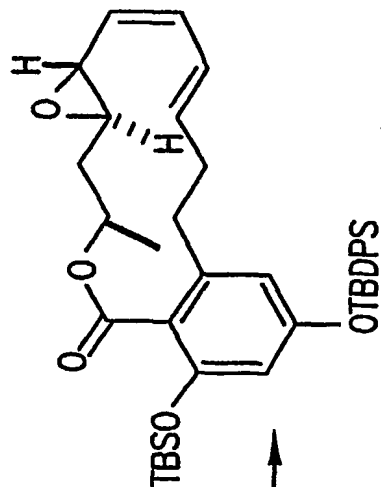


FROM FIG. 12-1

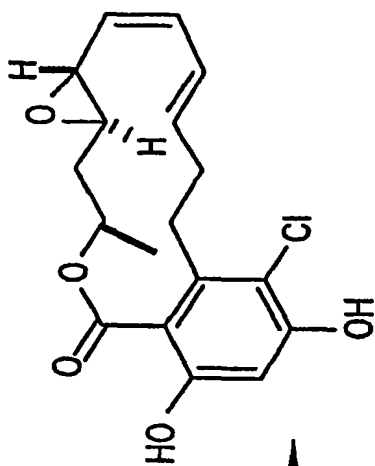
FIG. 12-2



1. Rainey Ni

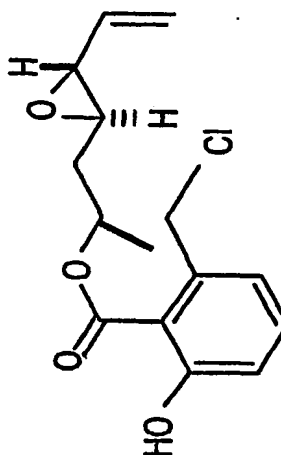
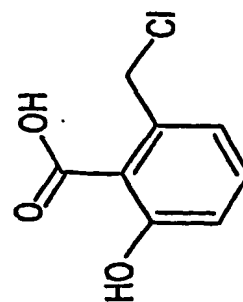


51

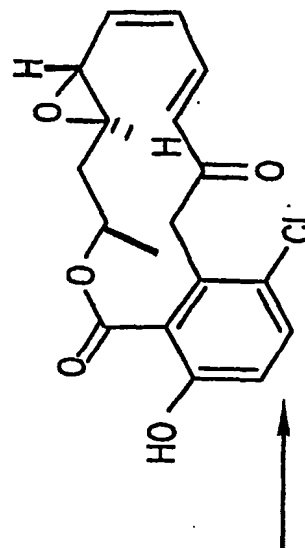


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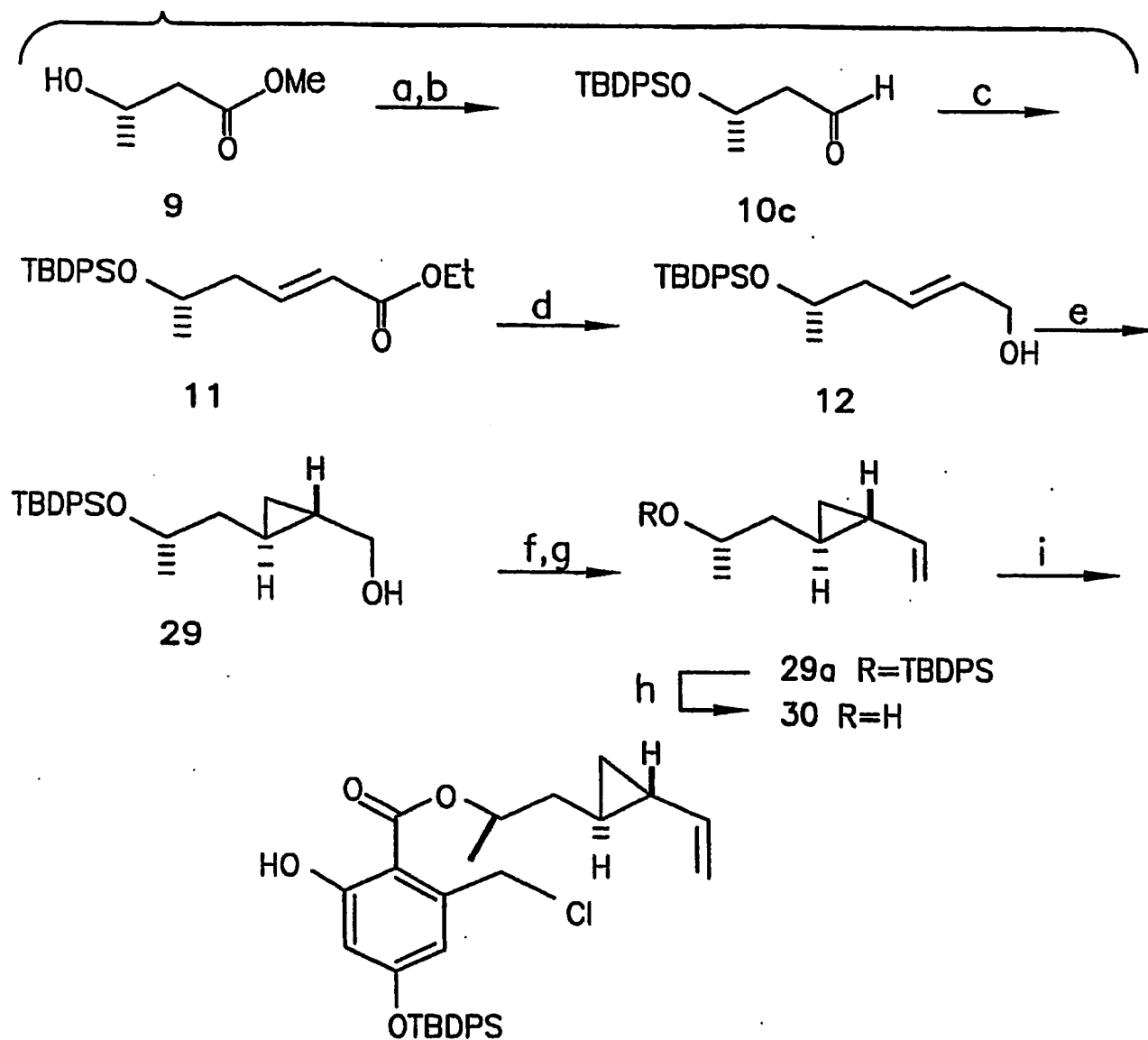
53



54

FIG. 13

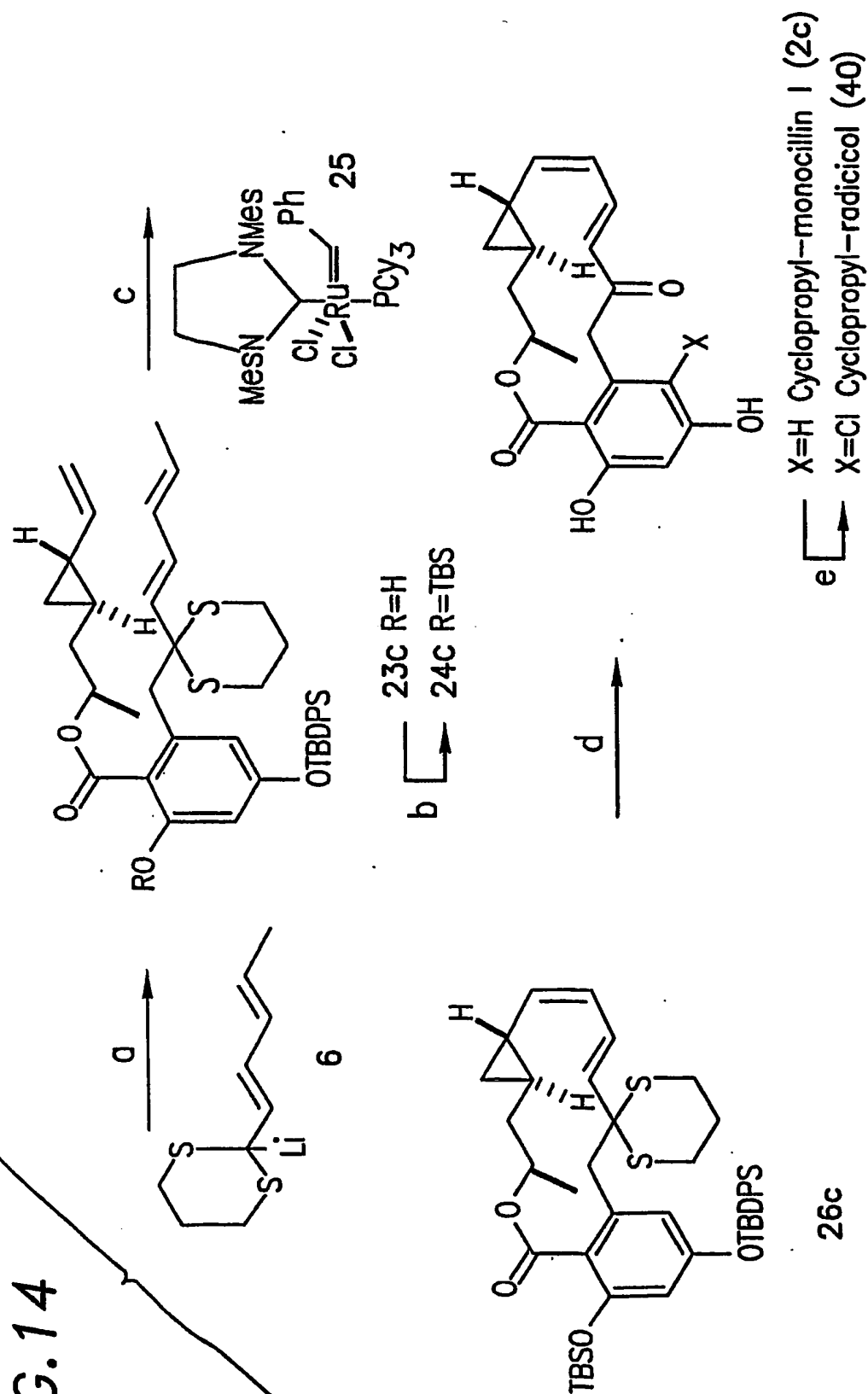
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- ^a (a) TBDPSCI, imid., >95%; (b) DIBAL-H, -78 °C, 92%; (c) LiCl, DIPEA (EtO)₂P(O)CH₂CO₂Et, 95%; (d) DIBAL-H -20 °C, 96%; (e) (+)-tetramethyltartaric acid diamide-BBu, Et₂Zn, CH₂I₂, 9 >95% ee; (f) SO₃*pyridine, Et₃N, DMSO, 90%; (g) Ph₃PCH NaHMDS, 0 °C, 82%; (h) TBAF, 89%; (i) 7, P(furyl)₃, DIA benzene, 60%

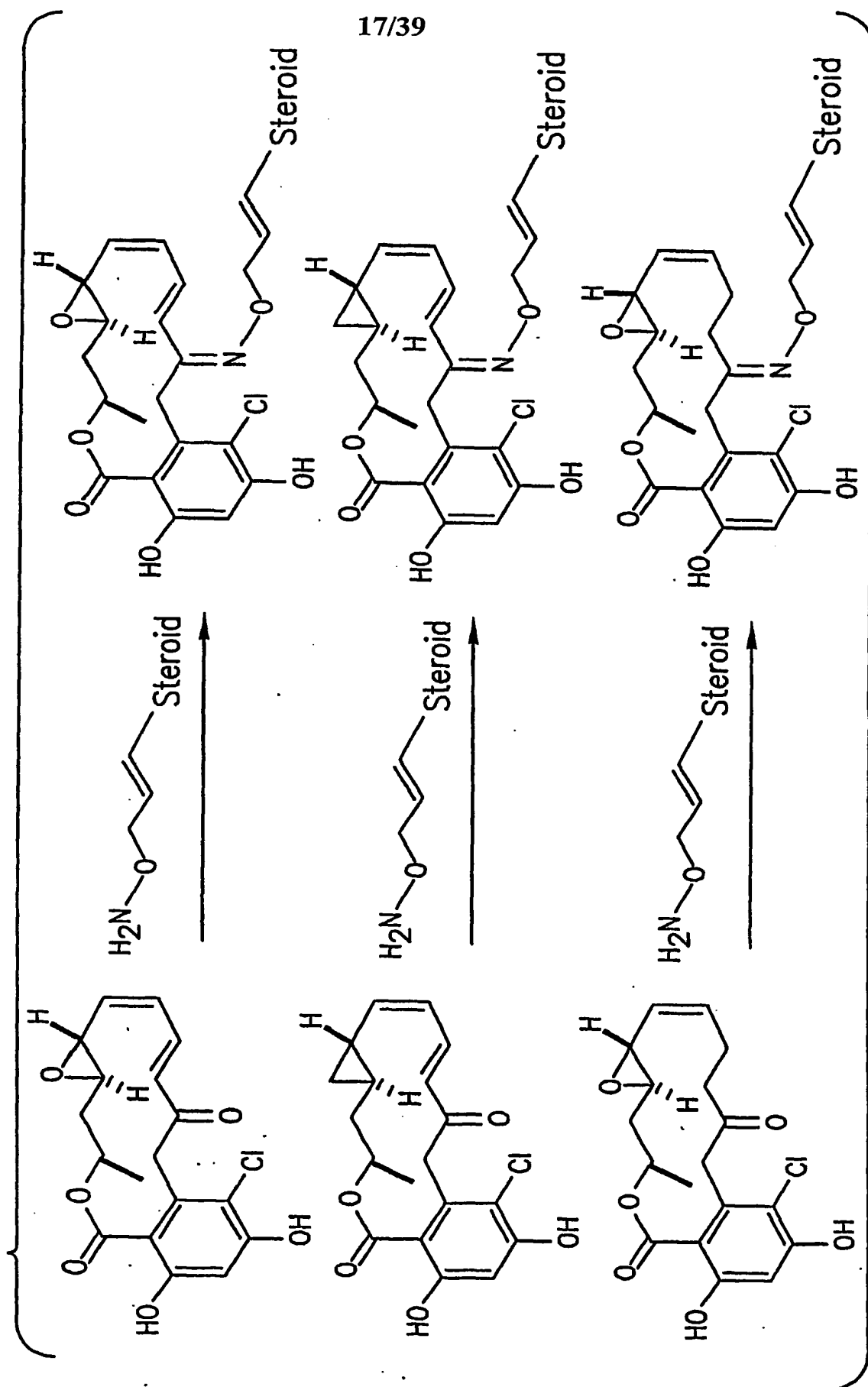
16/39

FIG. 14



a. $n\text{-BuLi}$, -78°C , 75% (3:1); b. TBSCl, 83%; c. 42°C , 20%; d. (i) mCPBA, (ii) Ac_2O , Et_3N , H_2O , 60°C , (iii) NaHCO_3 , MeOH, 60%; e. SO_2Cl_2 , 80%

FIG. 15-1



TO FIG. 15-2

FROM FIG. 15-1

FIG. 15-2

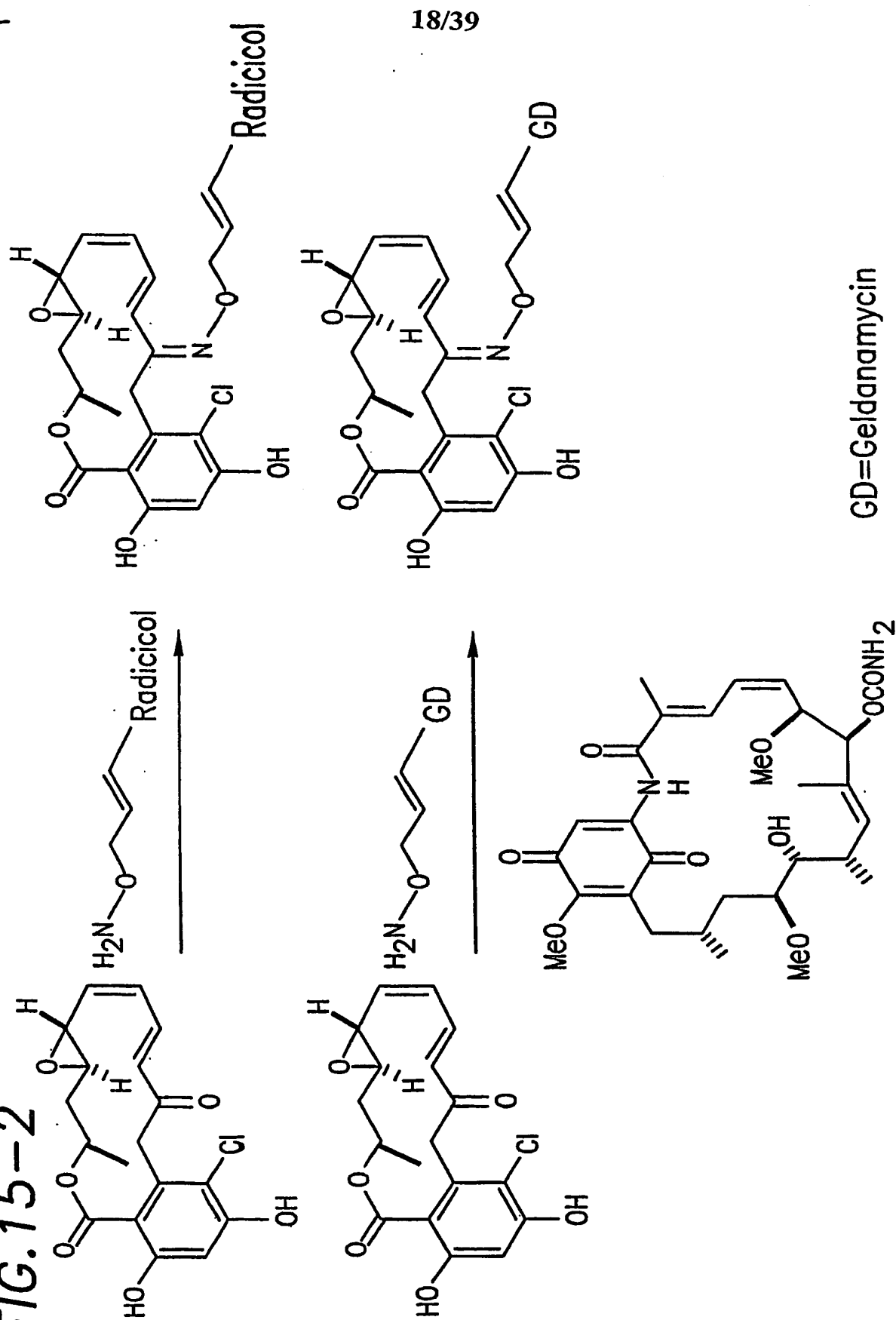
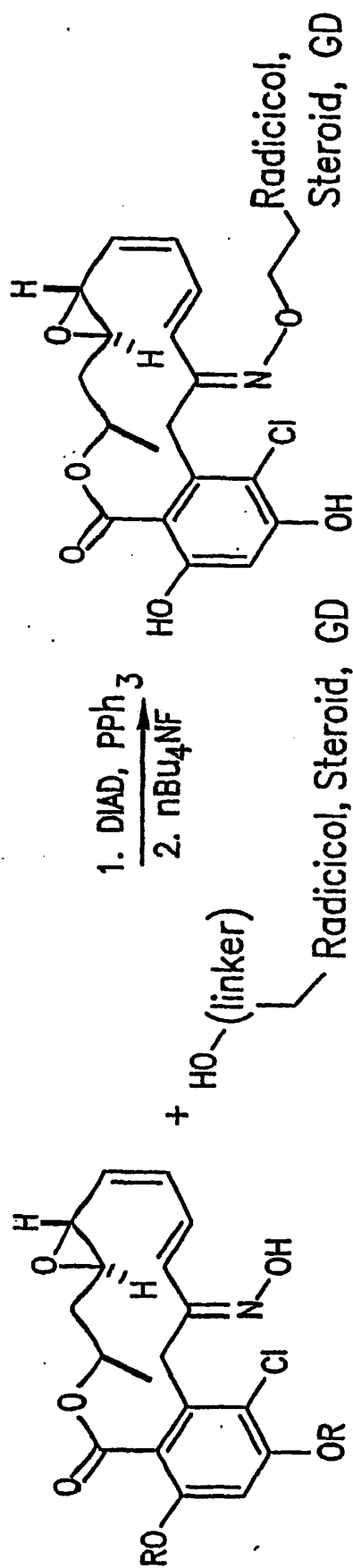
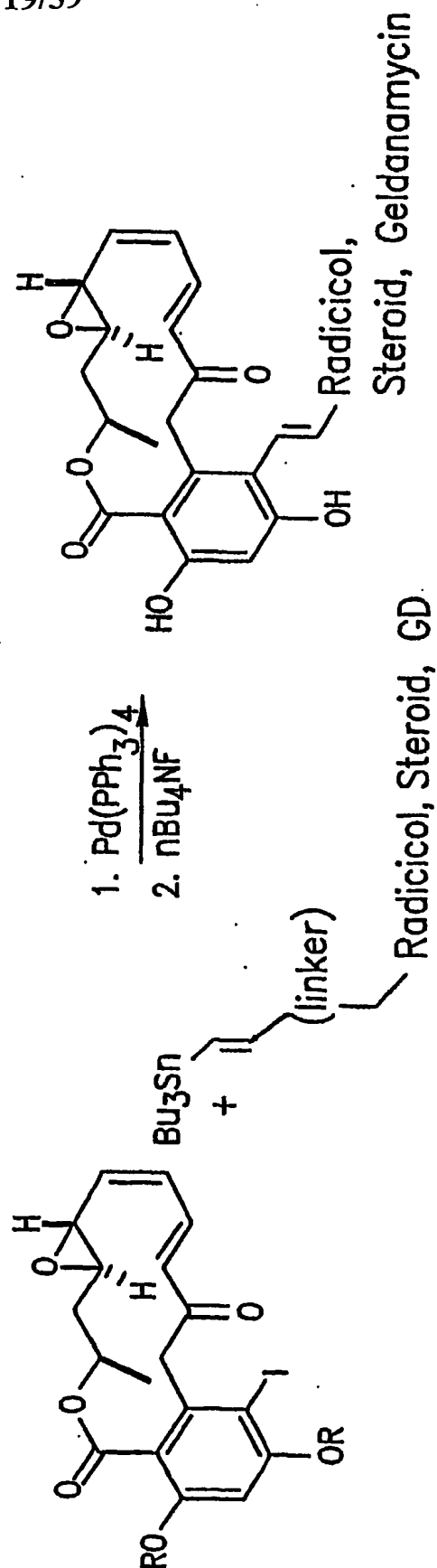


FIG. 16-1



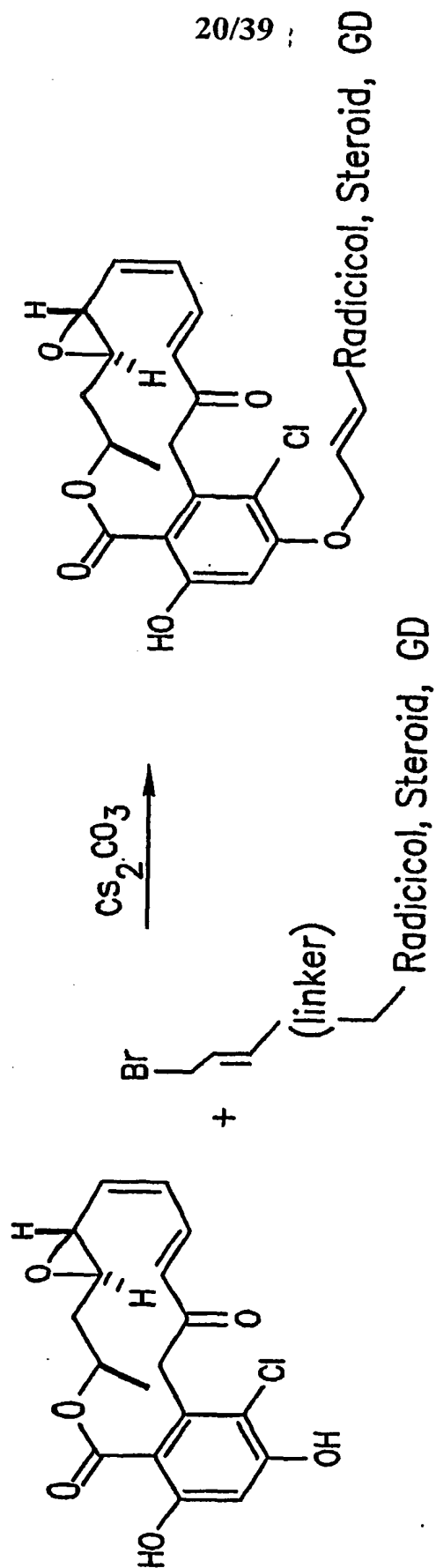
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TO FIG. 16-2

FROM FIG. 16-1

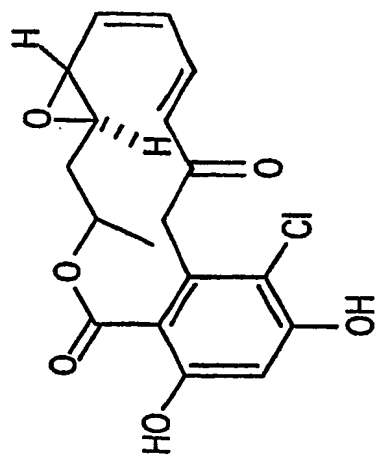
FIG. 16-2



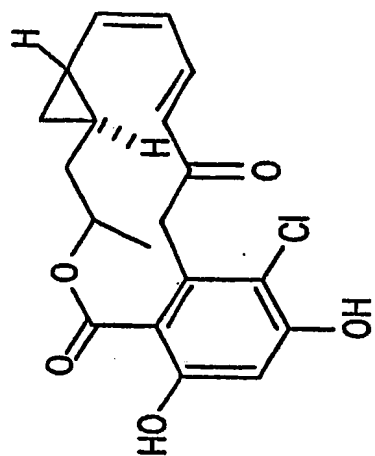
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FIG. 17-1

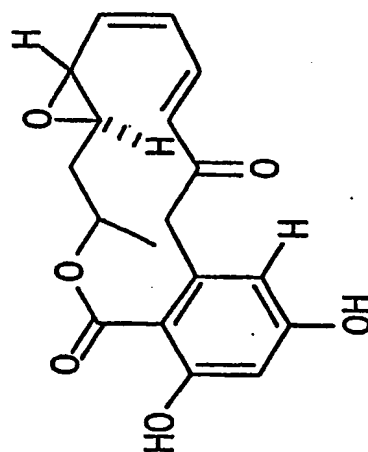
I. Radicicol



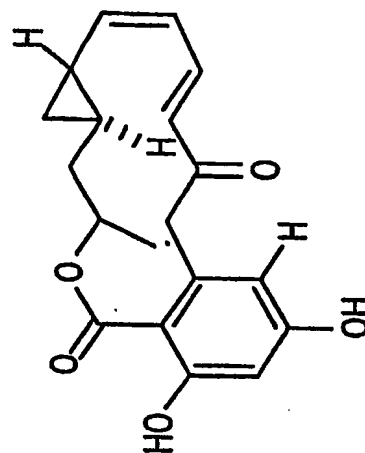
III. Cyclopropyl radicicol



II. Monocillin I



IV. Cyclopropyl monocillin

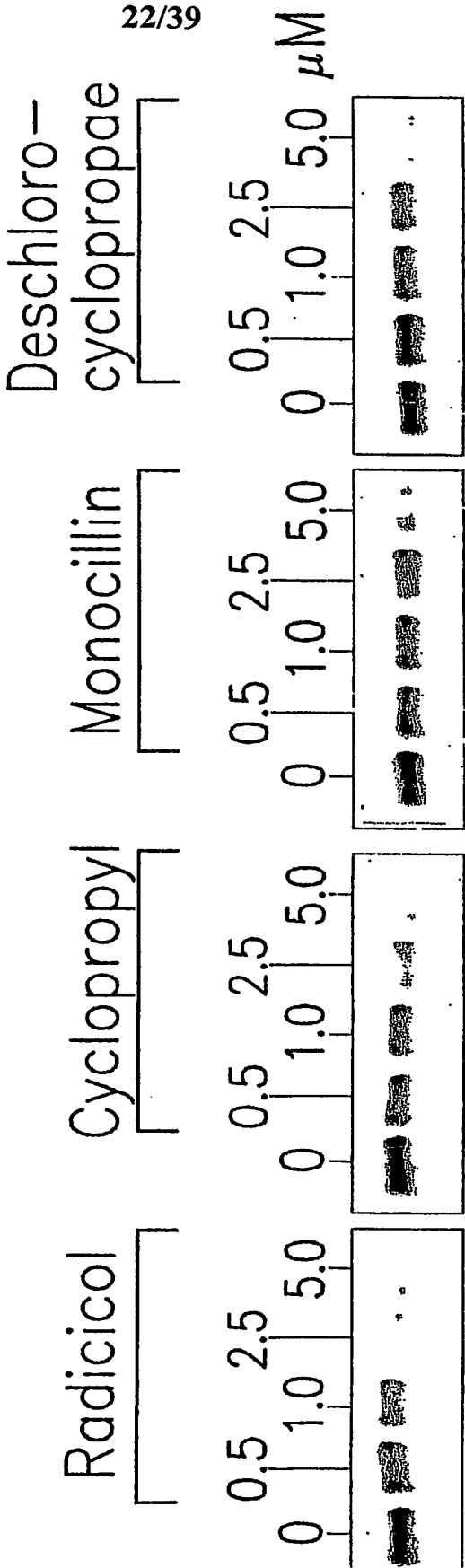


TO FIG. 17-2

FROM FIG. 17-1

FIG.17-2

MCF7 Cells Treated with Radicicol and Analogues



HER2

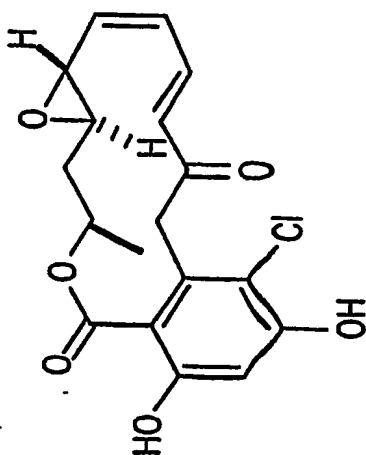
TO FIG. 17-3

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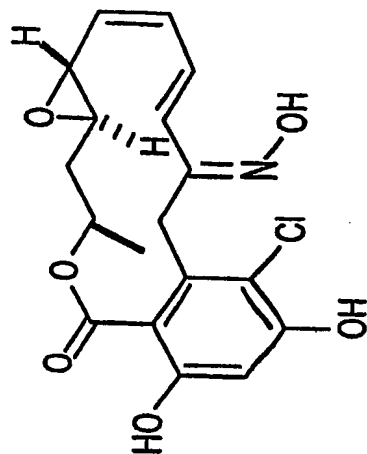
FROM FIG. 17-2

FIG. 17-3

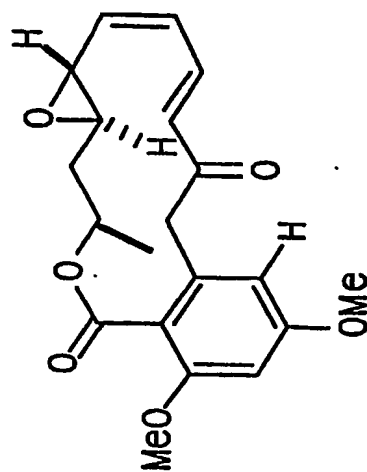
I. Radical



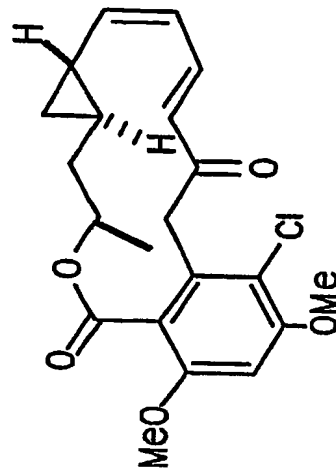
VII. Radical Oxime



V. Dimethyl Monocillin I



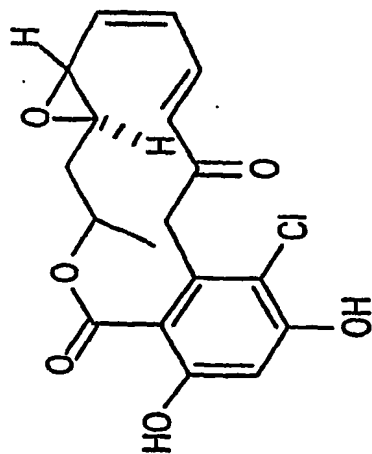
VI. Dimethyl Radical



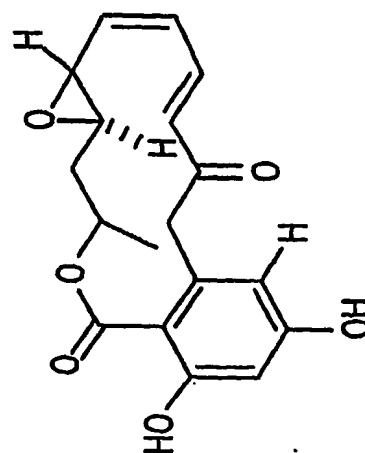
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FIG. 18-1

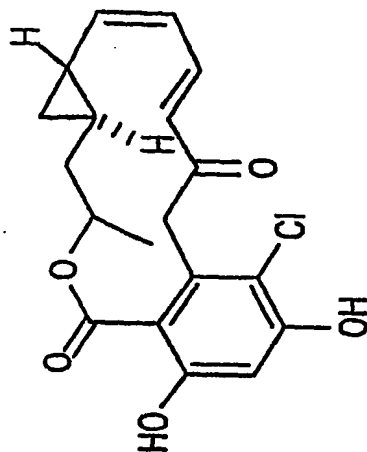
I. Radical



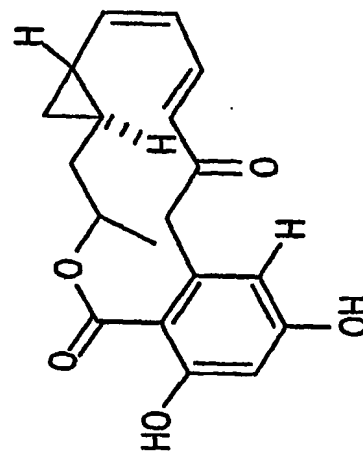
II. Monocillin I



III. Cyclopropyl radical



IV. Cyclopropyl monocillin

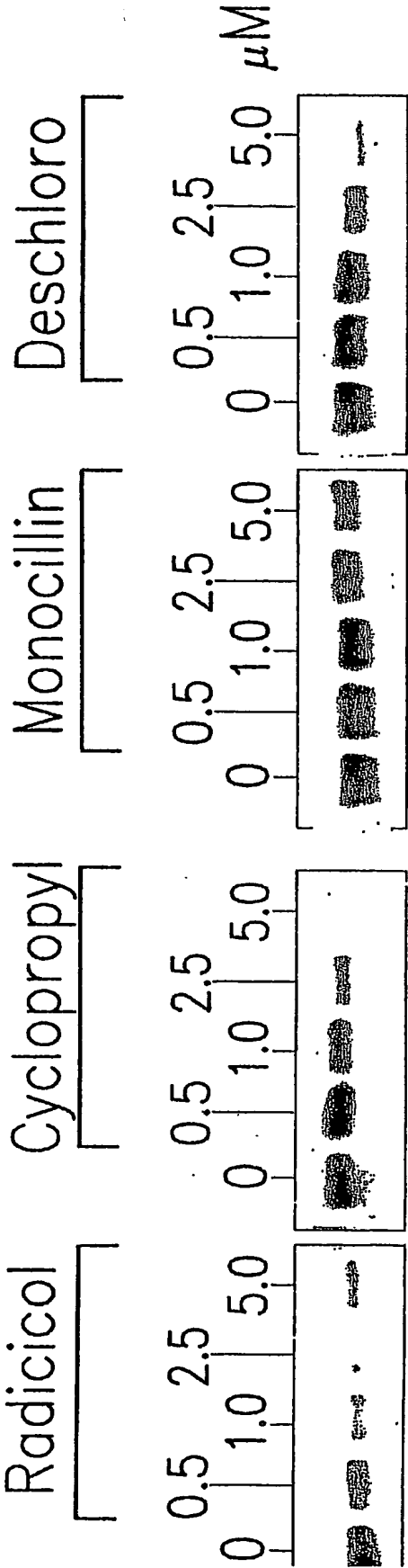


TO FIG. 18-2

FROM FIG. 18-1

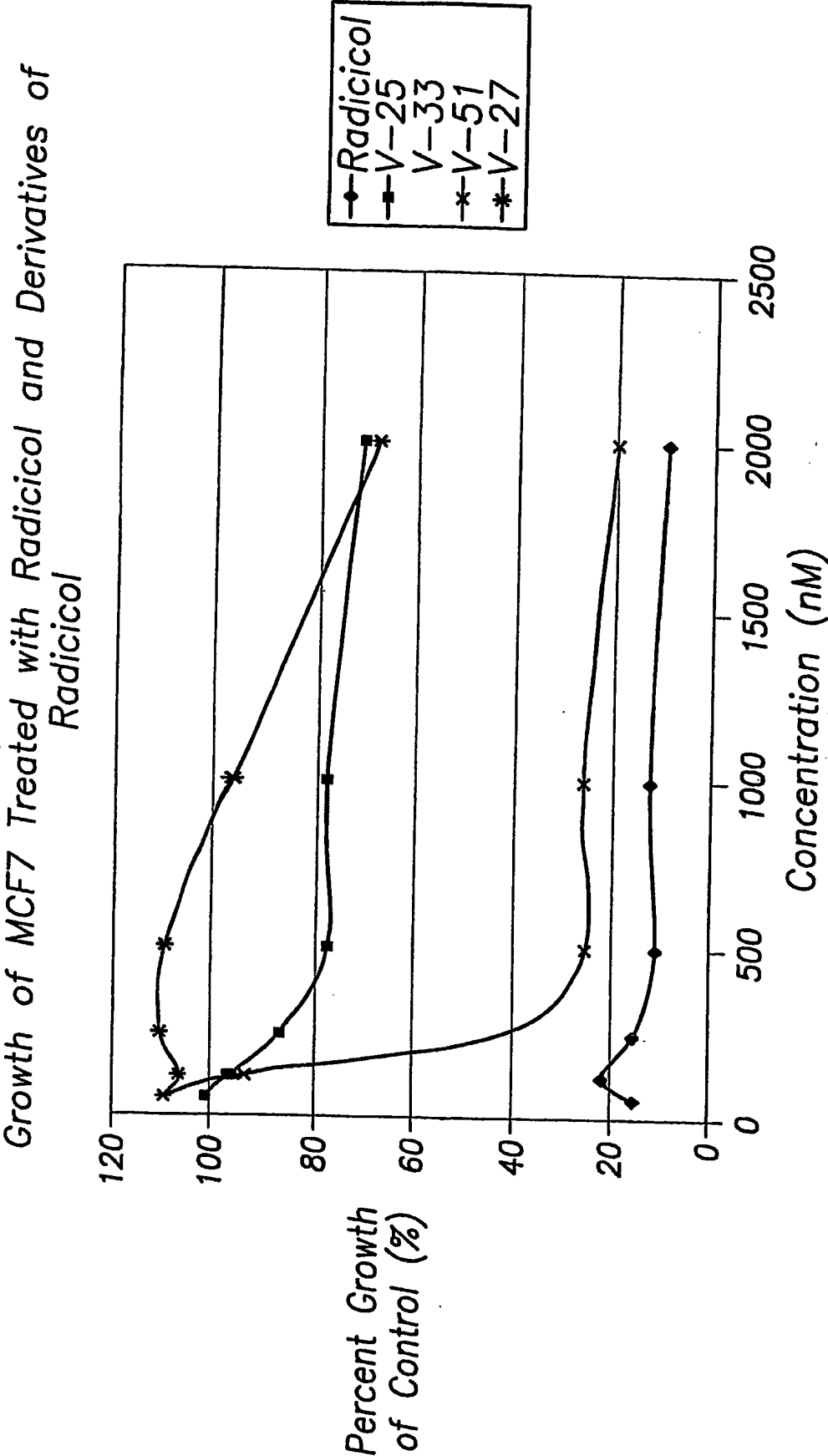
FIG. 18-2

BT474 Cells Treated with Novel Radicicoliols (24hrs.)



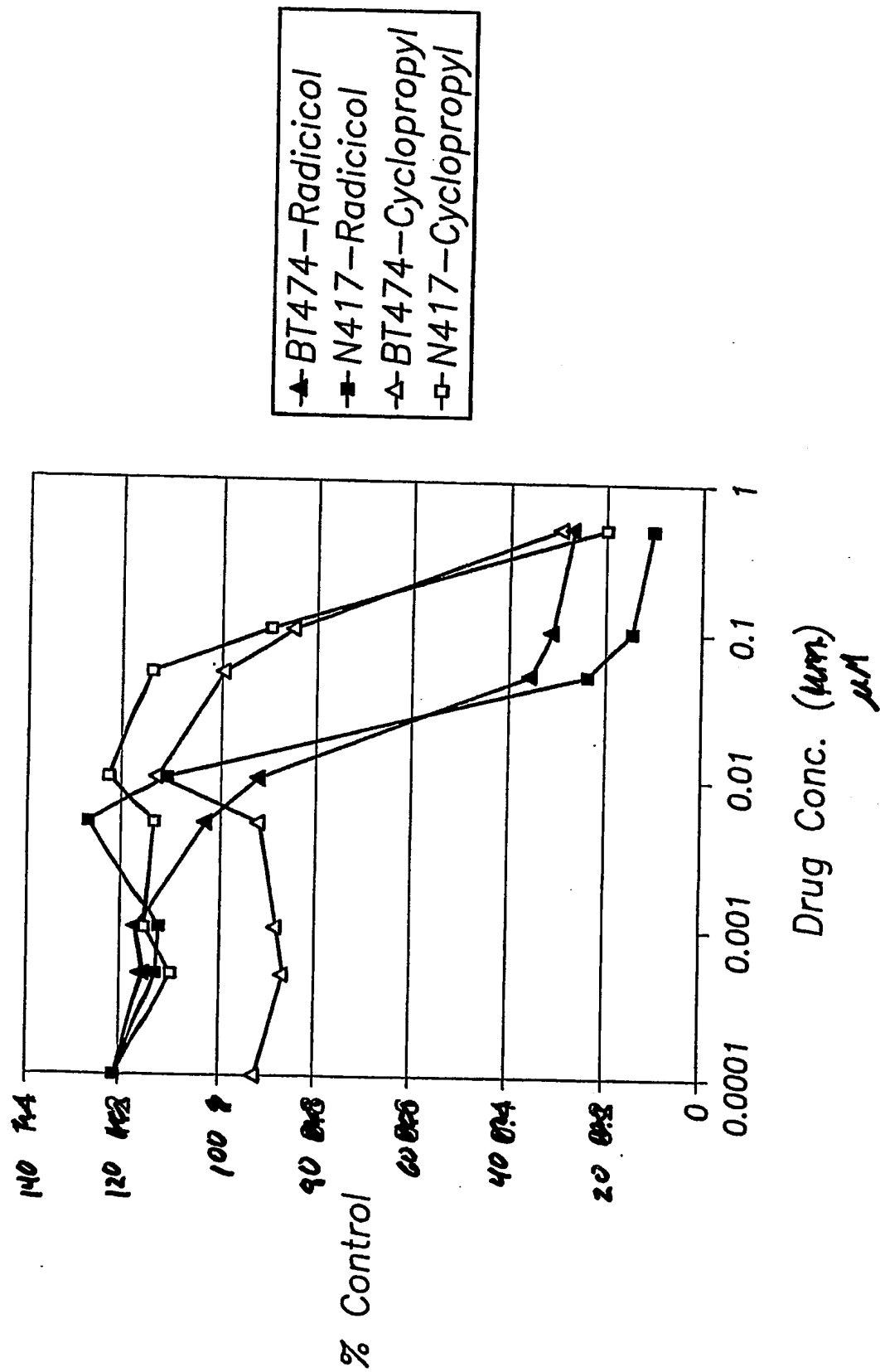
HER2

FIG. 19



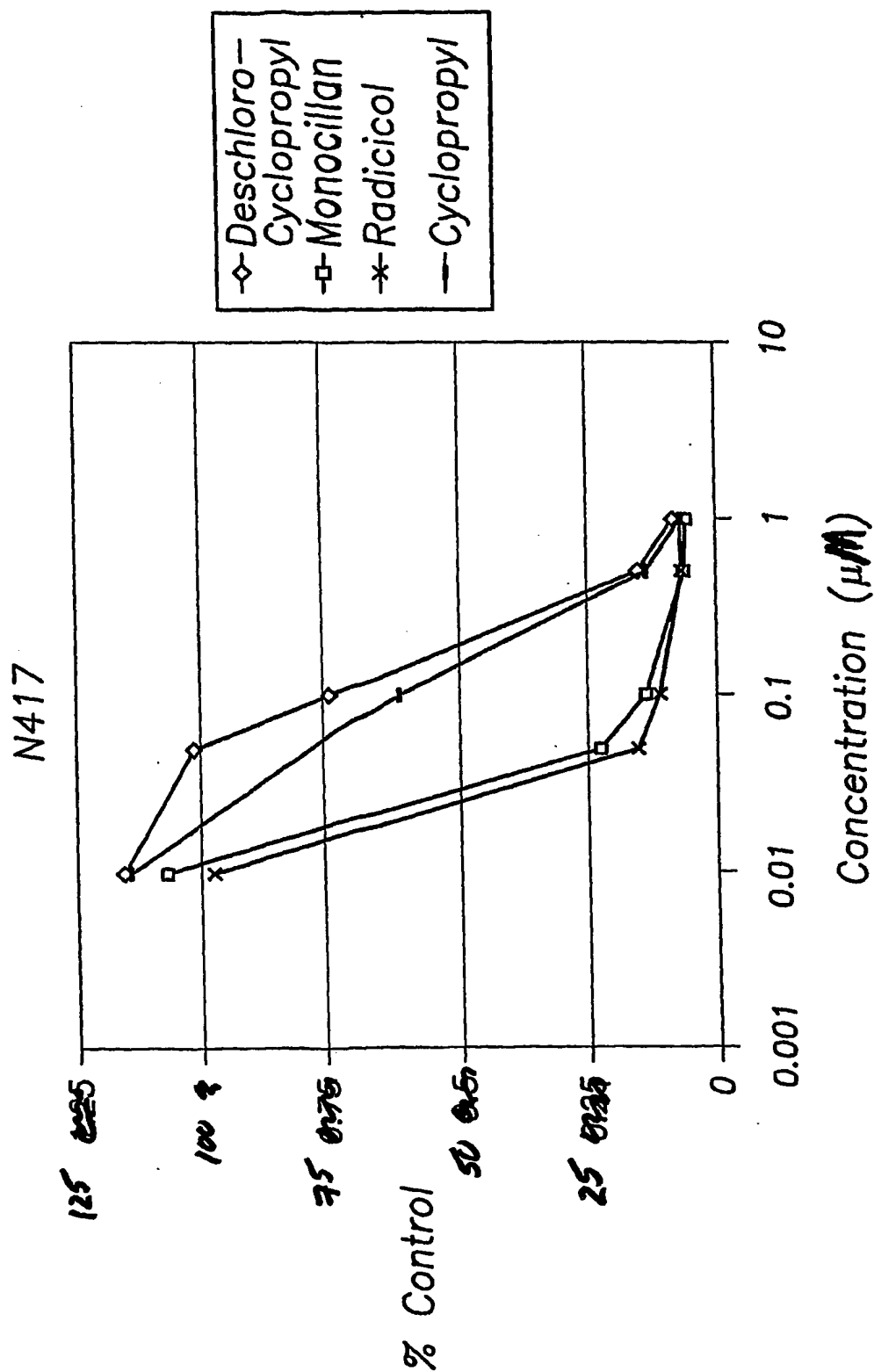
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FIG. 20



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FIG. 21



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Therapeutic effect of Cycloproparadicol in nude mice bearing human mammary carcinoma MX-1 xenograft (Q2Dx6, iv.injection)

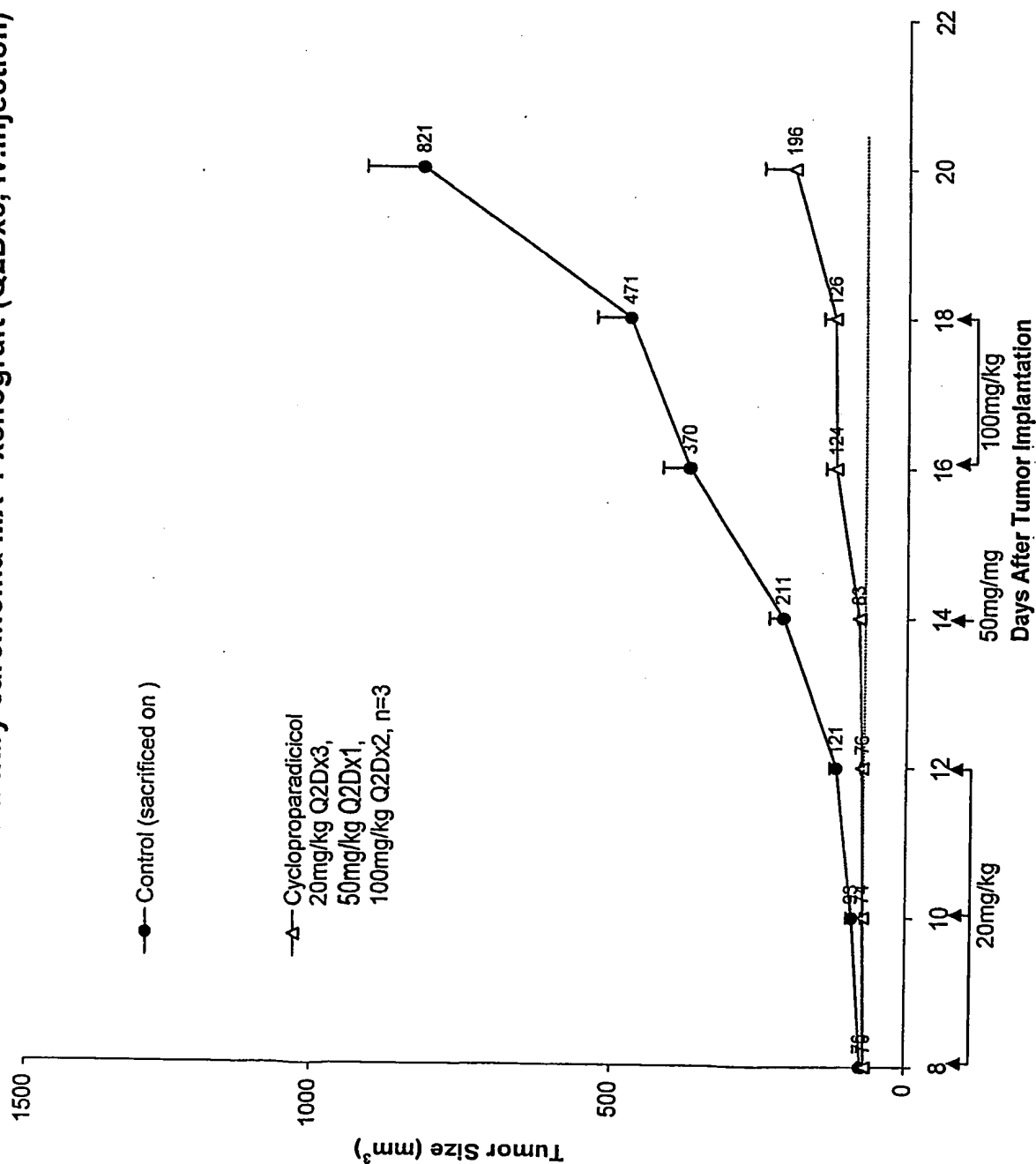


Fig. 22

Body weight changes of nude mice bearing human mammary carcinoma MX-1 xenograft:
Treatment with Cycloproparadicol (Q2Dx6, iv.injection)

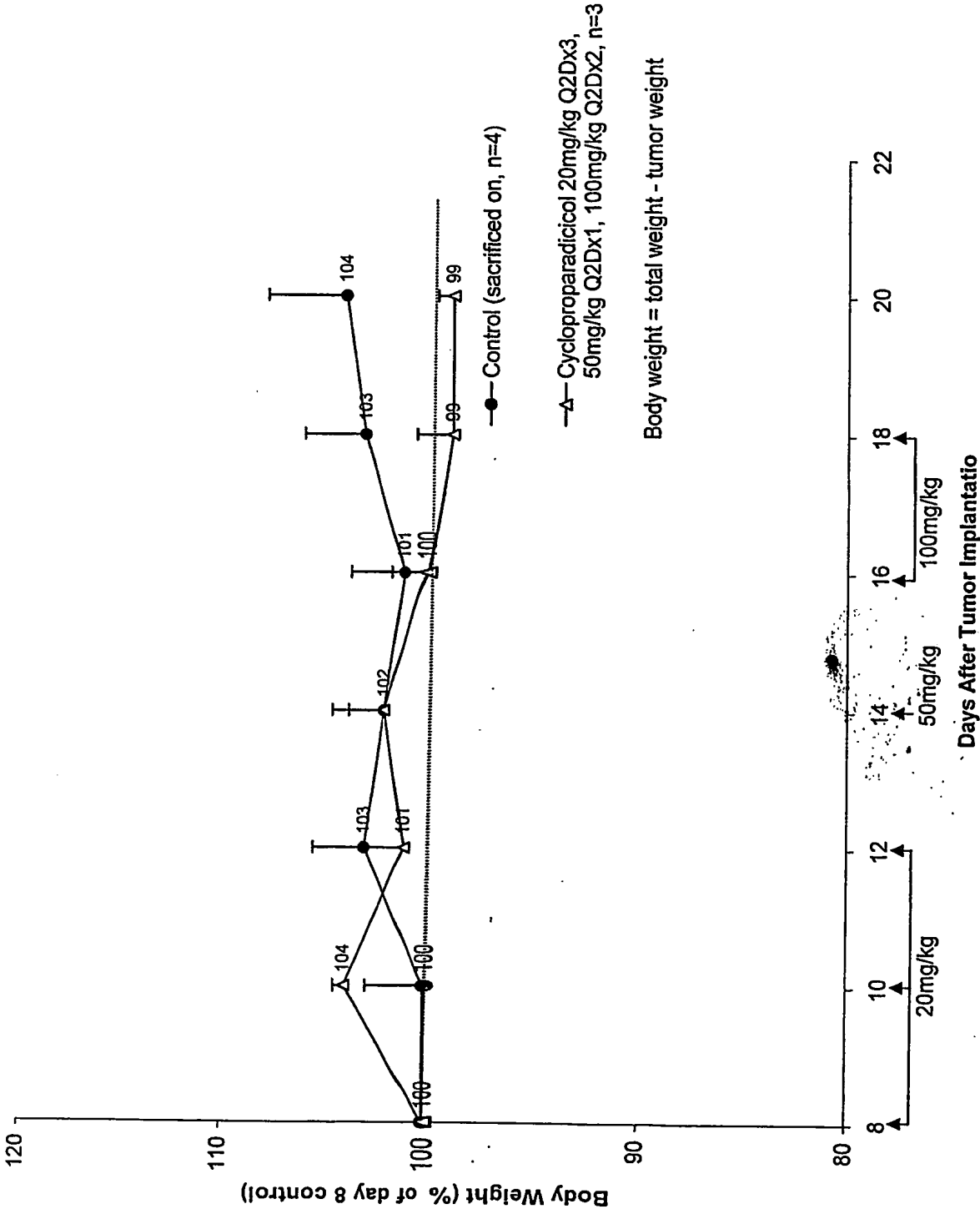


Fig 23

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Therapeutic effect of Radicolol & Cycloproparadicol in nude mice bearing human colon carcinoma (HCT-116) xenograft (QDx7, 4hr. iv-infusion)

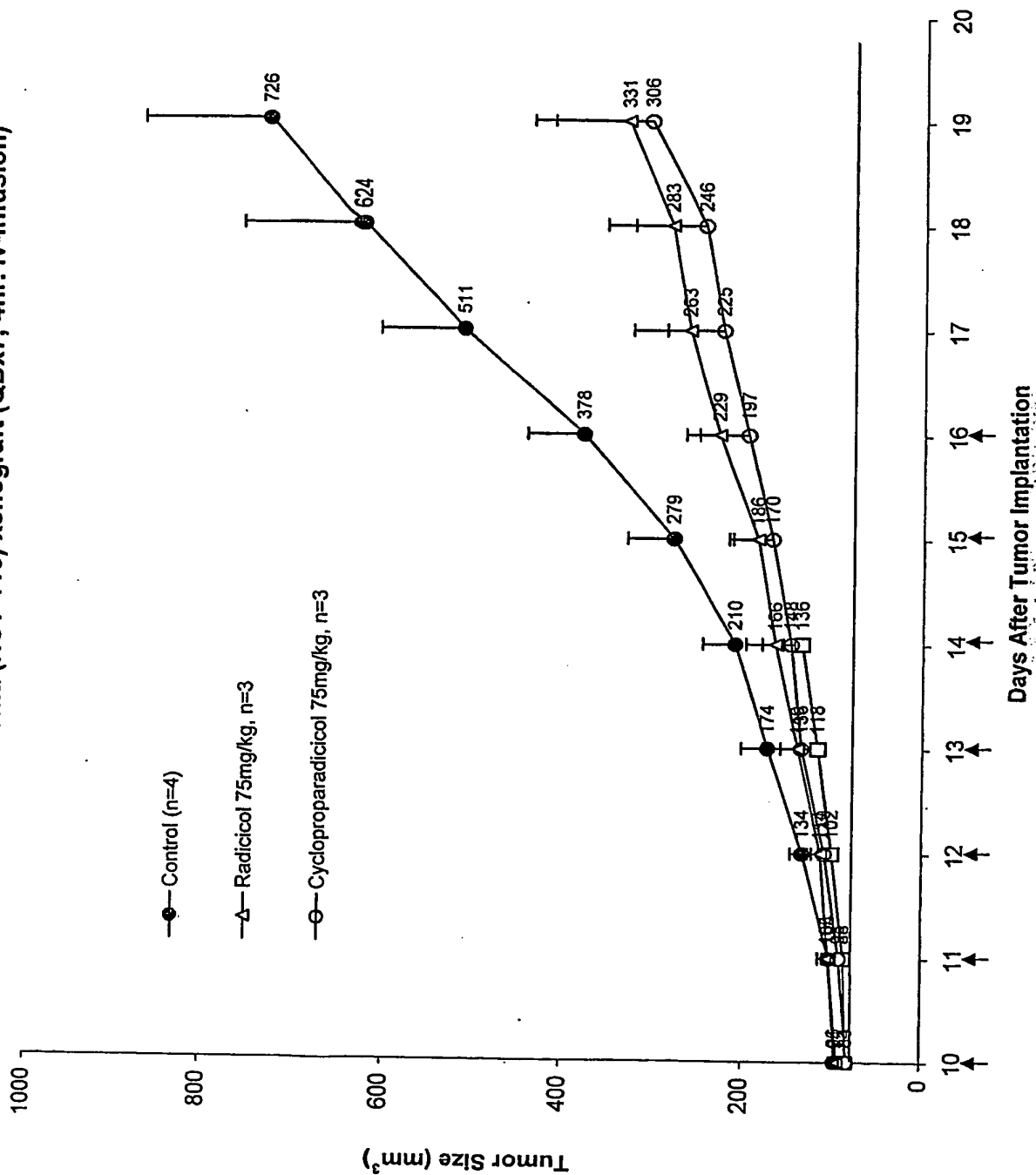


Fig. 24

Body weight changes of human colon carcinoma (HCT-116) xenograft bearing nude mice following treatment with Radicolol & Cycloproparadicolol (QDx7, 4hr. iv-infusion)

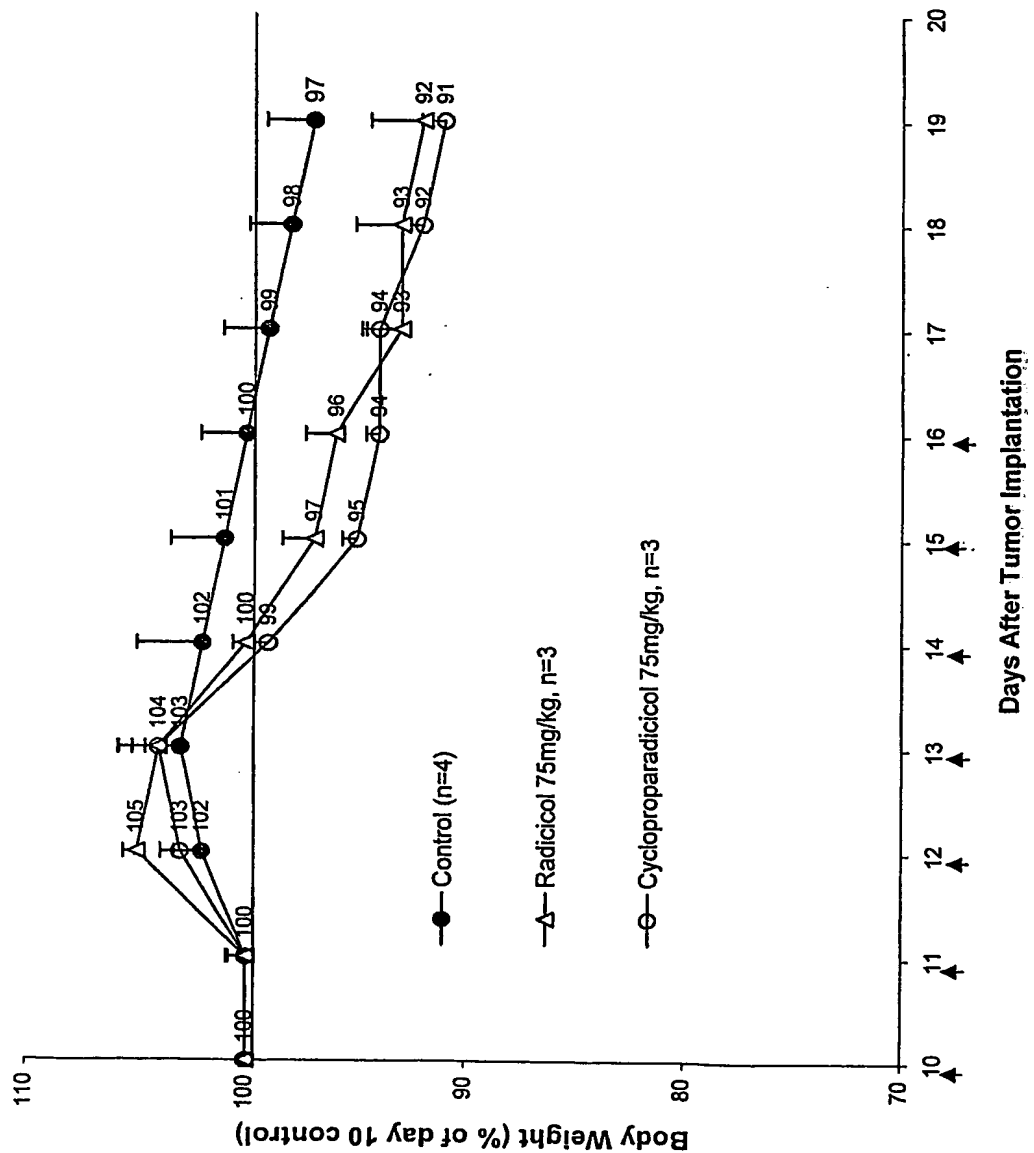


Fig. 25

MX-1 tumors
12 hrs following a 6 hr CIVI

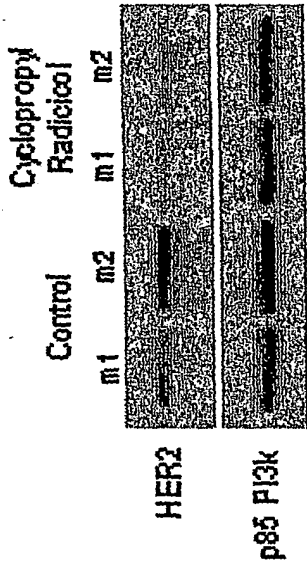


Fig. 26

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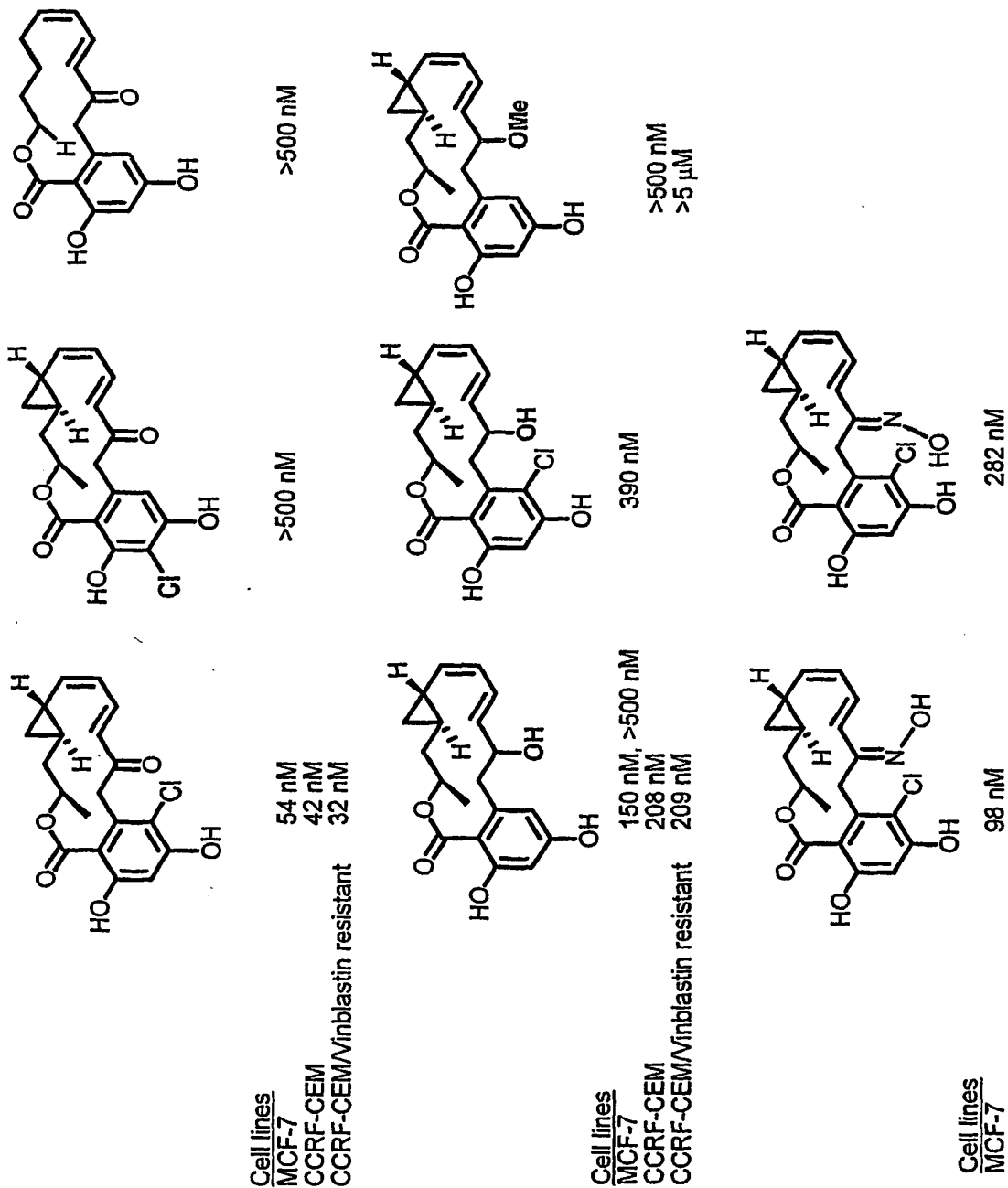
IC₅₀ of Growth Inhibition of Different Tumor Cell lines

Fig. 27

Degradation of HER2 by
Cycloproparadicicol Analogues

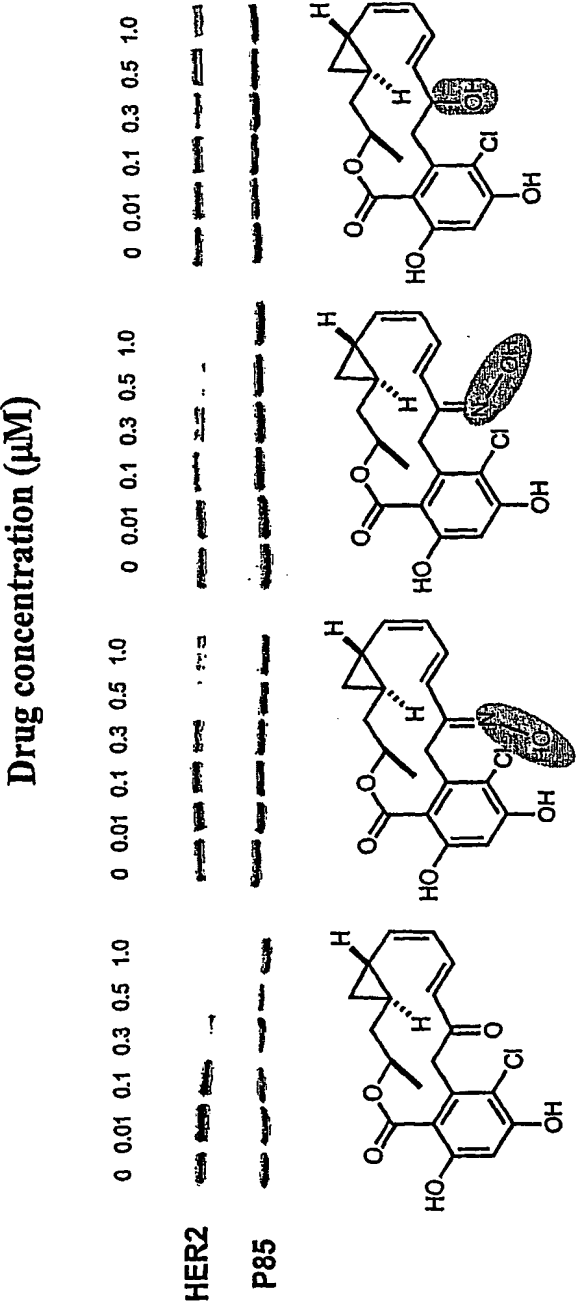


Fig. 28

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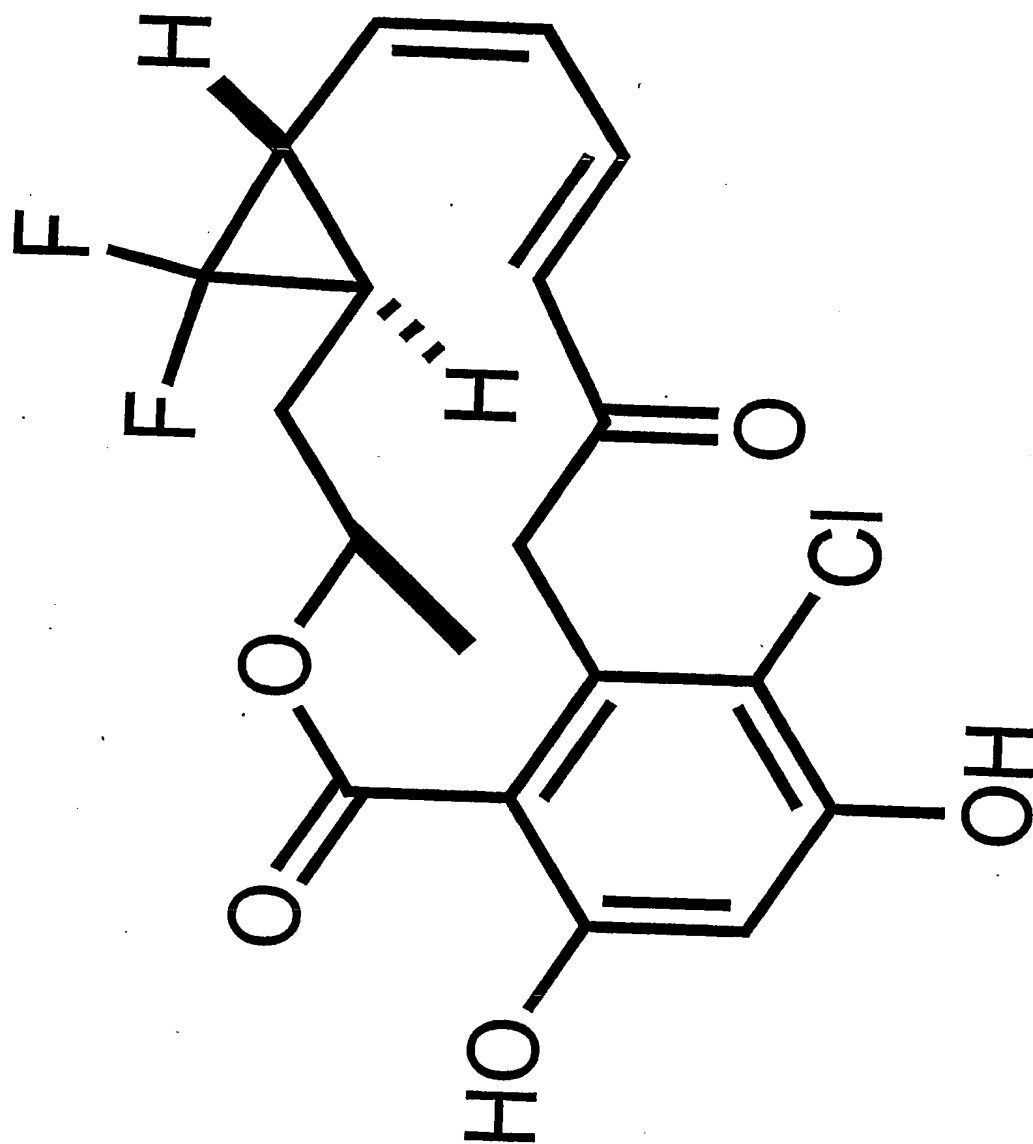
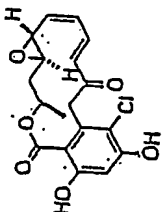
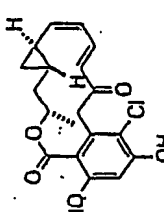
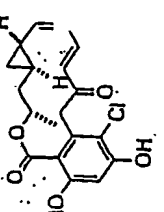
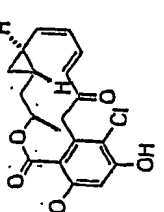
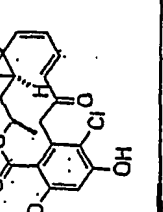


Fig. 29

Cytotoxic effect on CCRF-CEM cell growth by radicicol analogs^a.

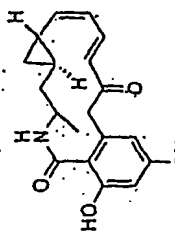
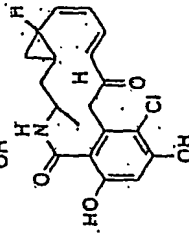
Compound	Structure	Cell growth inhibition (IC ₅₀ in μ M) ^b		
		CCRF-CEM	CCRF-CEM/VBL ^c	CCRF-CEM/taxol ^c
Radicicol (Sigma)		0.055 [±] 0.03	0.099 [1.8x]	0.070 [1.3x]
Cyclopropyl 1		4.81	9.84 [2.0x]	7.74 [1.6x]
Cyclopropyl 2		2.34	4.89 [2.1x]	2.89 [1.2x]
Cyclopropyl 3		0.58 [±] 0.13	0.87 [1.5x]	0.53 [0.9x]
Cyclopropyl 4 (Cycloproparadicicol)		0.055 [±] 0.04	0.041 [0.75x]	0.070 [1.3x]

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Fig. 30A

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Cytotoxic effect on CCRF-CEM cell growth by radicicol analogs^a. (Cont'd)

Compound	Structure	Cell growth inhibition (IC ₅₀ in μ M) ^b		
		CCRF-CEM	CCRF-CEM/VBL ^c	CCRF-CEM/taxol ^c
DechloroCyclopropa- radicicol Lactam		>10	>10	ND
Cycloproparadicicol Lactam		>5	>5	ND

^a Compounds of radicicol and cycloproparadicicol stereoisomers.^b Cell growth inhibition was measured by XTT tetrazonium assay after 72-hour incubation for cell growth. (Chou et al., Proc. Natl. Acad. Sci. USA 95: 15798-15802, 1998). Five to eight concentrations for each drug were used. IC₅₀ values were determined from dose-effect curves by using a computer program CalcuSyn for Windows by Chou and Hayball (Biosoft, Cambridge, UK, 1997).^c CCRF-CEM/VBL and CCRF-CEM/taxol are the CCRF-CEM sublines that are 320-fold and 42-fold resistant to vinblastine and taxol, respectively. Number in brackets is the fold of resistance of each drug when comparing the IC₅₀ values with those of the parent cell line, CCRF-CEM. The results showed that radicicol and cycloproparadicicol stereoisomers are not cross-resistant to vinblastine (typical MDR-Pgp substrate) nor to Taxol.

Fig. 30B

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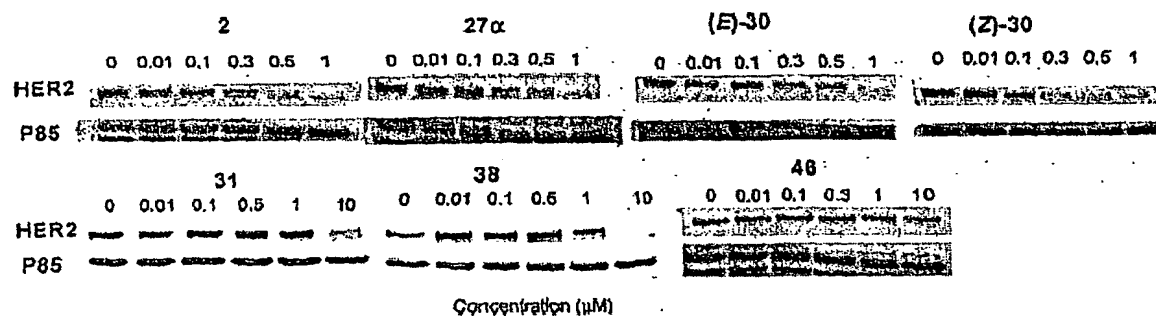


Figure 31: Her2 Degradation Assay

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